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(57) Abstract

Provided are novel benzothiepines, derivatives, and analogs thereof; pharmaceutical compositions containing them; and methods of using these compounds and compositions in medicine, particularly in the prophylaxis and treatment of hypertipidemic conditions such as those associated with atherosclerosis or hypercholesterolemia, in mammals.

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NOVEL BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

This application claims the benefit of priority of U.S. Provisional Application No. 60/013,119, filed March 11, 1996, which is a continuation in part of U.S. Serial No. 08/___,___, filed August 21, 1995, which is a continuation-in-part of U.S. Serial No. 08/305,526 filed September 12, 1994, both now pending.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel benzothiepines, derivatives and analogs thereof, pharmaceutical compositions containing them, and their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as is associated with atherosclerosis or hypercholesterolemia, in mammals.

Description of Related Art

It is well-settled that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction leads to an improvement in the disease state of

atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et Biophysica Acta, 1210 (1994) 255-287 discusses the biochemistry, physiology and known active agents surrounding bile acids and cholesterol.

Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", Gastroenterology, 1982:83:804-11.

In fact, cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal enterohepatic circulation (Reihnér, E. et al, in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein receptor expression in gallstone patients", Journal of Lipid Research, Volume 31, 1990, 2219-2226 and Suckling el al, "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", Atherosclerosis, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with

specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 25, pp. 18035-18046, 1993).

In a series of patent applications, eg Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents.

In vitro bile acid transportinhibition is disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds"

Selected benzothiepines are disclosed in world patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

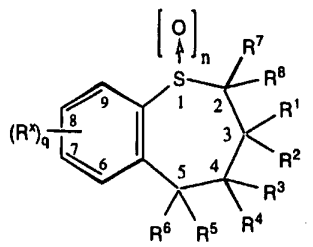
The above references show continuing efforts to find safe, effective agents for the prophylaxis and treatment of hyperlipidemic diseases and their usefulness as hypocholesterolemic agents.

Additionally selected benzothiepines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

The present invention furthers such efforts by providing novel benzothiepines, pharmaceutical compositions, and methods of use therefor.

SUMMARY OF THE INVENTION

Accordingly, among its various apects, the present invention provides compounds of formula (I):



(I)

wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^WA^-$, SR^9, $S^+R^9A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl

optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_1-C_{10} cycloalkylidene;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R' and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl,

cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S^-R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle

can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, P(O)R7, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heterocycle, quaternary heteroaryl, and quaternary heteroarylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, P(O)R', phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13}, R^{14}, and R^{15} are optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, PO(OR16)OR17, $P^+R^9R^{10}A^-$, $S^+R^9A^-$, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M, and p is 0 or 1; or

R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring;

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heterocycle, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13}, $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, NR"C(O)R", $C(O)NR^{13}R^{14}$, NR14C(O)R13, C(O)OM, COR^{13}, OR^{18}, $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR")OR"$, $P^+R^9R^{11}R^{12}A^-$, $S^+R'R"A^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, P(O)R13, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or P(O)R';

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR")OR"$, $S^+R"R"A^-$, and $N^+R^9R^{11}R^{12}A^-$,

provided that both R^5 and R^6 cannot be hydrogen, OH, or SH and when R^5 is OH, R^1, R^2, R^3, R^4, R^7 and R^8 cannot be all hydrogen;

provided that when R^3 or R^4 is phenyl, only one of R^1 or R^2 is H;

provided that when q = 1 and R^x is styryl, anilido, or anilinocarbonyl, only one of R^1 or R^4 is alkyl; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferably, R^5 and R^6 can independently be selected from the group consisting of H, aryl, heterocycle, quaternary heterocycle, and quaternary heteroaryl,

wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, P(O)R7, $P^+R^7R^8A^-$, or phenylene,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and P(O)(OR')OR'.

More preferably, R' or R' has the formula:

$$-Ar-(R')_t$$

wherein:

t is an integer from 0 to 5;

Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; and

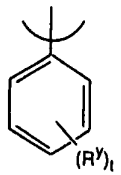
one or more R^y are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S'R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR')OR'$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene.

Most preferably, R^5 or R^6 has the formula (II):



(II)

The invention is further directed to a compound selected from among:

$R^{20} - R^{19} - R^{21}$ (Formula DI)

$$R^{20} - R^{19} - R^{21} \quad \text{(Formula DII)},$$

and

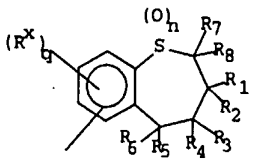
$$R^{22}$$
$$|$$
$$R^{20} - R^{19} - R^{21} \quad \text{(Formula DIII)}$$
$$|$$
$$R^{23}$$

wherein R^{19} is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can optionally have one or more carbon atoms replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, quatarnary heterocycle, quaternary heteroaryl, or aryl,

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR^{11})OR^{14}$, $S^+R^{11}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$;

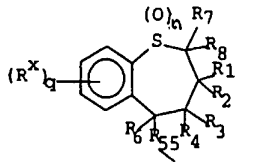
wherein R^{19} further comprises functional linkages by which R^{19} is bonded to R^{20}, R^{21}, or R^{22} in the compounds of Formulae DII and DIII, and R^{23} in the compounds of Formula DIII. Each of R^{20}, R^{21}, or R^{22} and R^{23} comprises a benzothiepine moiety as described above that is therapeutically effective in inhibiting ileal bile acid transport.

The invention is also directed to a compound selected from among Formula DI, Formula DII and Formula DIII in which each of R^{20}, R^{21}, R^{22} and R^{23} comprises a benzothiepine moiety corresponding to the Formula:



(Formula DIV)

or:



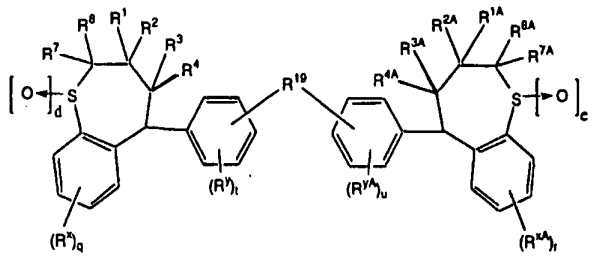
(Formula DIVA)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^x, q, and n are as defined in Formula I as described above, and R^{55} is either a covalent bond or arylene.

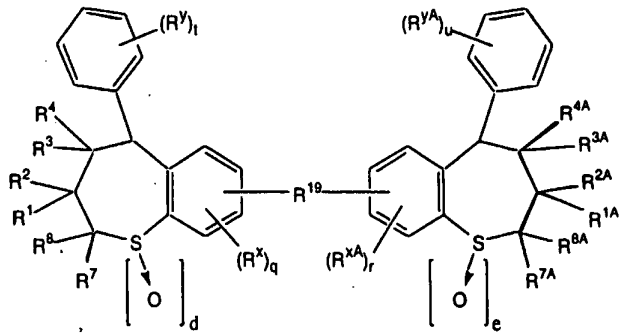
In compounds of Formula DIV, it is particularly preferred that each of R^{20}, R^{21}, and R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII, be bonded at its 7-

or 8-position to R^{19}. In compounds of Formula DIVA, it is particularly preferred that R^{55} comprise a phenylene moiety bonded at a *m*- or *p*-carbon thereof to R^{19}.

Examples of Formula DI include:

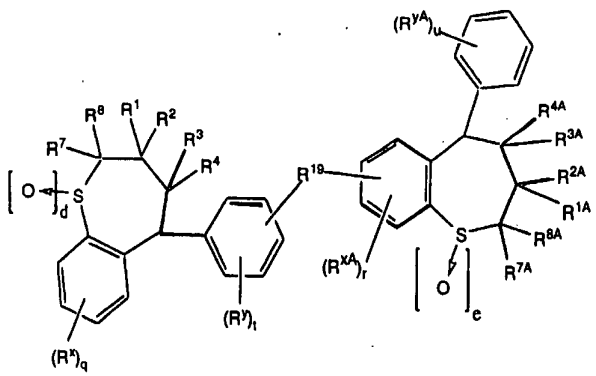


(III)



(IV)

and



(V)

In any of the dimeric or multimeric structures discussed immediately above, benzothiepine compounds of the present invention can be used alone or in various combinations.

In any of the compounds of the present invention, R^1 and R^2 can be ethyl/butyl or butyl/butyl.

In another aspect, the present invention provides a pharmaceutical composition for the prophylaxis or treatment of a disease or condition for which a bile acid transport inhibitor is indicated, such as a hyperlipidemic condition, for example, atherosclerosis. Such compositions comprise any of the compounds disclosed above, alone or in combination, in an amount effective to reduce bile acid levels in the blood, or to reduce transport thereof across digestive system membranes, and a pharmaceutically acceptable carrier, excipient, or diluent.

In a further aspect, the present invention also provides a method of treating a disease or condition in

mammals, including humans, for which a bile acid transport inhibitor is indicated, comprising administering to a patient in need thereof a compound of the present invention in an effective amount in unit dosage form or in divided doses.

In yet a further aspect, the present invention also provides processes for the preparation of compounds of the present invention.

Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed dscription and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will beomce apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the emobodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

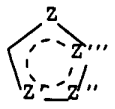
Definitions

In order to aid the reader in understanding the following detailed description, the following definitions are provided:

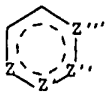
"Alkyl", "alkenyl," and "alkynyl" unless otherwise noted are each straight chain or branched chain hydrocarbons of from one to twenty carbons for alkyl or two to twenty carbons for alkenyl and alkynyl in the present invention and therefore mean, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl respectively and isomers thereof.

"Aryl" means a fully unsaturated mono- or multi-ring carbocyle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

"Heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms can be replaced by N, S, P, or O. This includes, for example, the following structures:



or



wherein Z, Z', Z" or Z"' is C, S, P, O, or N, with the proviso that one of Z, Z', Z" or Z"' is other than carbon, but is not O or S when attached to another Z

atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z', Z" or Z"' only when each is C.

The term "heteroaryl" means a fully unsaturated heterocycle.

In either "heterocycle" or "heteroaryl," the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

The term "quaternary heterocycle" means a heterocycle in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heterocycle to the molecule of interest can be at a heteroatom or elsewhere.

The term "quaternary heteroaryl" means a heteroaryl in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heteryaryl to the molecule of interest can be at a heteroatom or elsewhere.

The term "halogen" means a fluoro, chloro, bromo or iodo group.

The term "haloalkyl" means alkyl substituted with one or more halogens.

The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to ten carbon atoms, and wherein any ring can contain one or more double or triple bonds.

The term "diyl" means a diradical moiety wherein said moiety has two points of attachment to molecules of interest.

The term "oxo" means a doubly bonded oxygen.

The term "polyalkyl" means a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "polyether" means a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "polyalkoxy" means a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "cycloaklylidene" means a mono- or multi-ringed carbocycle wherein a carbon within the ring structure is doubly bonded to an atom which is not within the ring structures.

The term "carbohydrate" means a mono-, di-, tri-, or polysaccharide wherein the polysaccharide can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan.

The term "peptide" means polyamino acid containing up to about 100 amino acid units.

The term "polypeptide" means polyamino acid containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid untis, most preferably from about 100 amino acid units to about 500 amino acid units.

The term "alkylammoniumalkyl" means a NH_4 group or a mono-, di- or tri-substituted amino group, any of

which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.

The term "triazolyl" includes all positional isomers. In all other heterocycles and heteroaryls which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocycles and heteroaryls.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

The term "active compound" means a compound of the present invention which inhibits transport of bile acids.

When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

The term "a bile acid transport inhibitor" means a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

Compounds

The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as

diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the compounds of the present invention.

The compounds of the present invention also include tautomers.

The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

Compound Syntheses

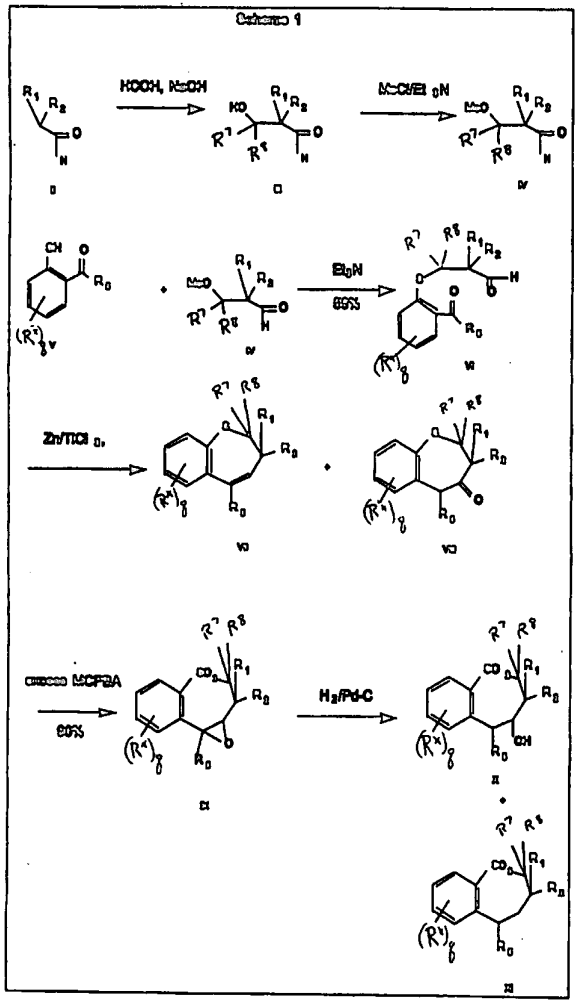
The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

Generally, the compounds of the present invention can be prepared by the procedures described below.

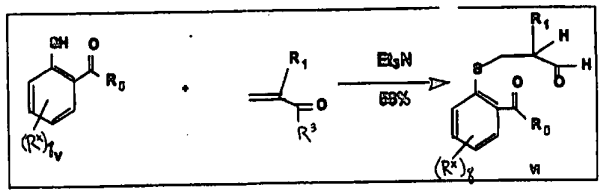
For example, as shown in Scheme I, reaction of aldehyde II with formaldehyde and sodium hydroxide yields the hydroxyaldehyde III which is converted to mesylate IV with methansulfonyl chloride and triethylamine similar to the procedure described in Chem. Ber. **98**, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described in WO 93/16055, in the presence of triethylamine yields keto-aldehyde VI which can be cyclized with the

reagent, prepared from zinc and titanium trichloride in refluxing ethylene glycol dimethyl ether (DME), to give a mixture of 2,3-dihydrobenzothiepine VII and two racemic steroisomers of benzothiepin-(5*H*)-4-one VIII when R^1 and R^2 are nonequivalent. Oxidation of VII with 3 equivalents of m-chloro-perbenzoic acid (MCPBA) gives isomeric sulfone-epoxides IX which upon hydrogenation with palladium on carbon as the catalyst yield a mixture of four racemic stereoisomers of 4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X and two racemic stereoisomers of 2,3,4,5-tetrahydro-benzothiepine-1,1-dioxides XI when R^1 and R^2 are nonequivalent.

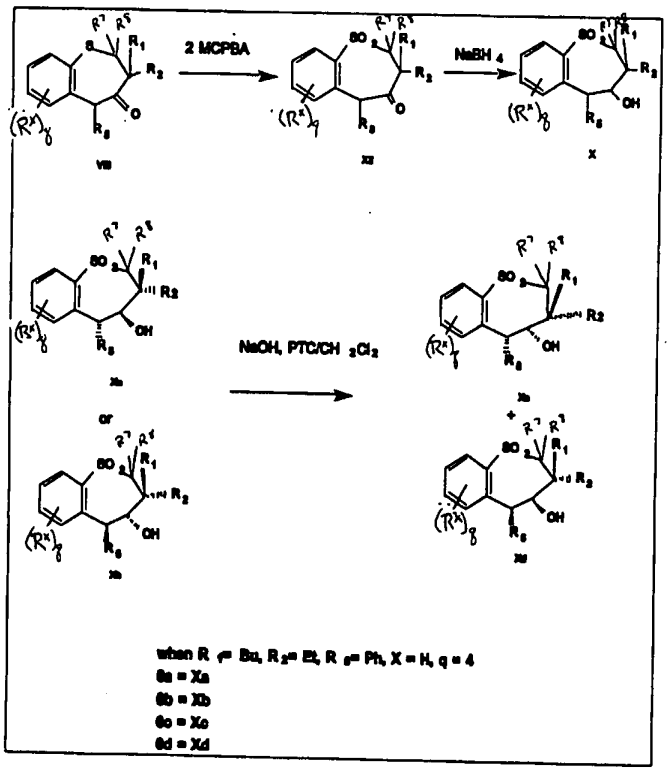
Optically active compounds of the present invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in *J. Org. Chem.*, **39**, 3904 (1974), *ibid.*, **42**, 2781 (1977), and *ibid.*, **44**, 4891 (1979).



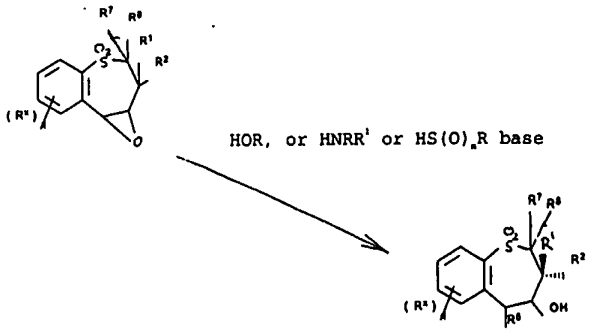
Alternatively, keto-aldehyde VI where R' is H can be prepared by reaction of thiophenol V with a 2-substituted acrolein.



Benzothiepin-(5*H*)-4-one VIII can be oxidized with MCPBA to give the benzothiepin-(5*H*)-4-one-1,1-dioxide XII which can be reduced with sodium borohydride to give four racemic stereoisomers of X. The two stereoisomers of X, Xa and Xb, having the OH group and R' on the opposite sides of the benzothiepine ring can be converted to the other two isomers of X, Xc and Xd, having the OH group and R' on the same side of the benzothiepine ring by reaction in methylene chloride with 40-50% sodium hydroxide in the presence of a phase transfer catalyst (PTC). The transformation can also be carried out with potassium t-butoxide in THF.



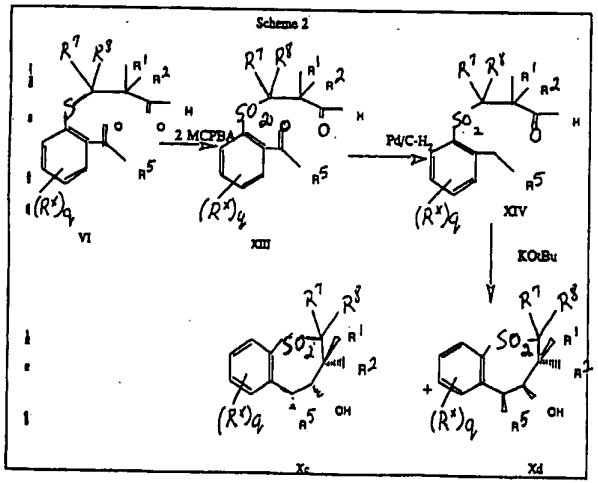
The compounds of the present invention where R³ is OR, NRR' and S(O)$_n$R and R⁴ is hydroxy can be prepared by reaction of epoxide IX where R³ is H with thiol, alcohol, and amine in the presence of a base.

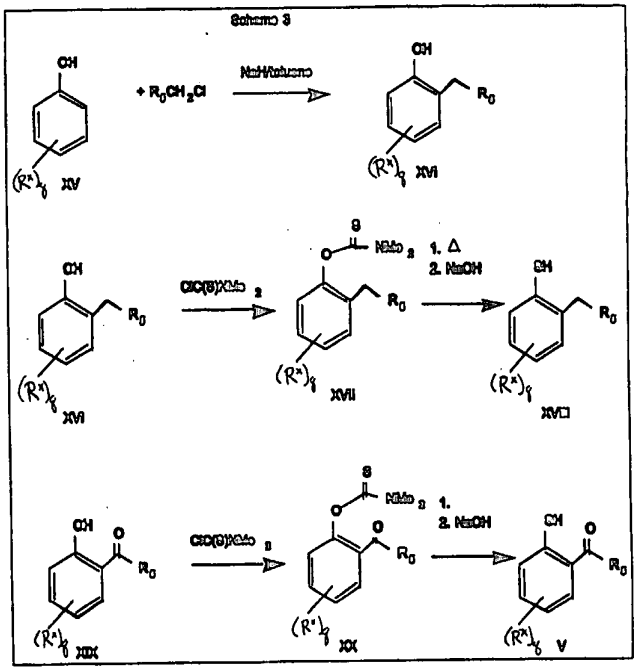


R^3 = OR, NRR', S(O)$_n$R

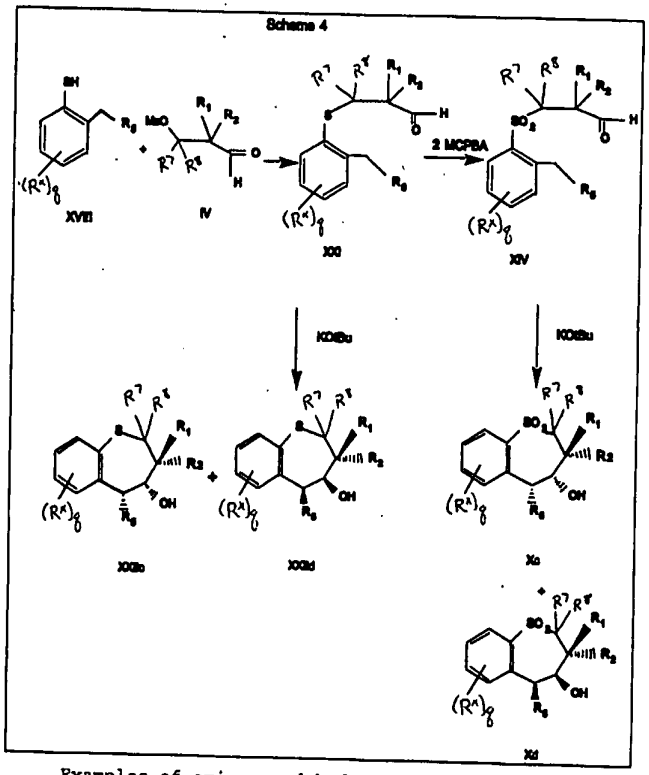
Another route to Xc and Xd of the present invention is shown in Scheme 2. Compound VI is oxidized to compound XIII with two equivalent of m-chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture of Xc and Xd. Separation of Xc and Xd can be accomplished by either HPLC or fractional crystallization.

The thiophenols XVIII and V used in the present invention can also be prepared according to the Scheme 3. Alkylation of phenol XV with an arylmethyl chloride in a nonpolar solvent according to the procedure in ***J. Chem. Soc.*, 2431-2432 (1958)** gives the ortho substituted phenol XVI. The phenol XVI can be converted to the thiophenol XVIII via the thiocarbamate XVII by the procedure described in ***J. Org. Chem.*, 31, 3980 (1966)**. The phenol XVI is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give thiocarbamate XVII which is thermally rearranged at 200-300 °C, and the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate thiocarbamate XX.



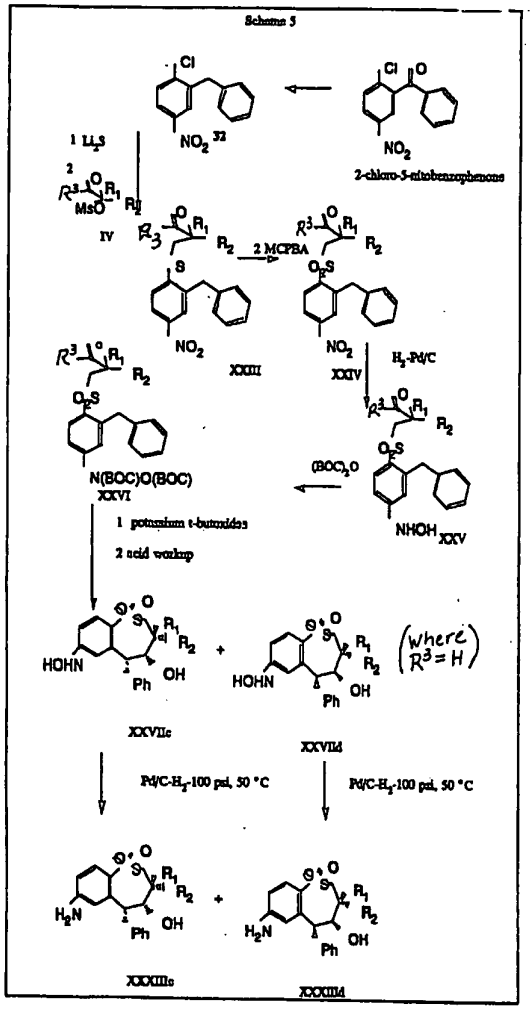


Scheme 4 shows another route to benzothiepine-1,1-dioxides Xc and Xd starting from the thiophenol XVIII. Compound XVIII can be reacted with mesylate IV to give the sulfide-aldehyde XXI. Oxidation of XXI with two equivalents of MCPBA yields the sulfone-aldehyde XIV which can be cyclized with potassium t-butoxide to a mixture of Xc and Xd. Cyclyzation of sulfide-aldehyde with potassium t-butoxide also gives a mixture of benzothiepine XXIIc and XXIId.

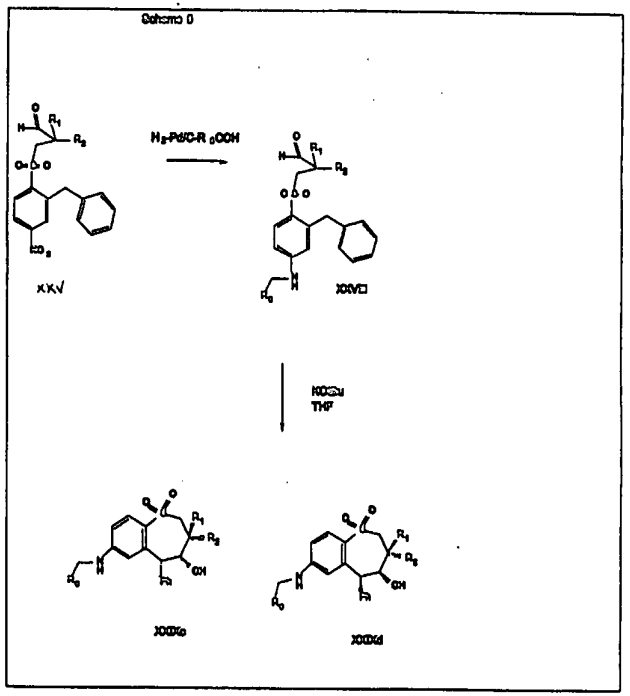


Examples of amine- and hydroxylamine-containing compounds of the present invention can be prepared as shown in Scheme 5 and Scheme 6. 2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane **32**. Reaction of **32** with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV which can be reduced by hydrogenation to the hydroxylamine XXV. Protecting the hydroxylamine XXV with di-t-butyldicarbonate gives the *N,O*-di-(t-

butoxycarbonyl)hydroxylamino derivative XXVI. Cyclization of XXVI with potassium t-butoxide and removal of the t-butoxycarbonyl protecting group gives a mixture of hydroxylamino derivatives XXVIIc and XXVIId. The primary amine XXXIIIc and XXXIIId derivatives can also be prepared by further hydrogenation of XXIV or XXVIIc and XXVIId.

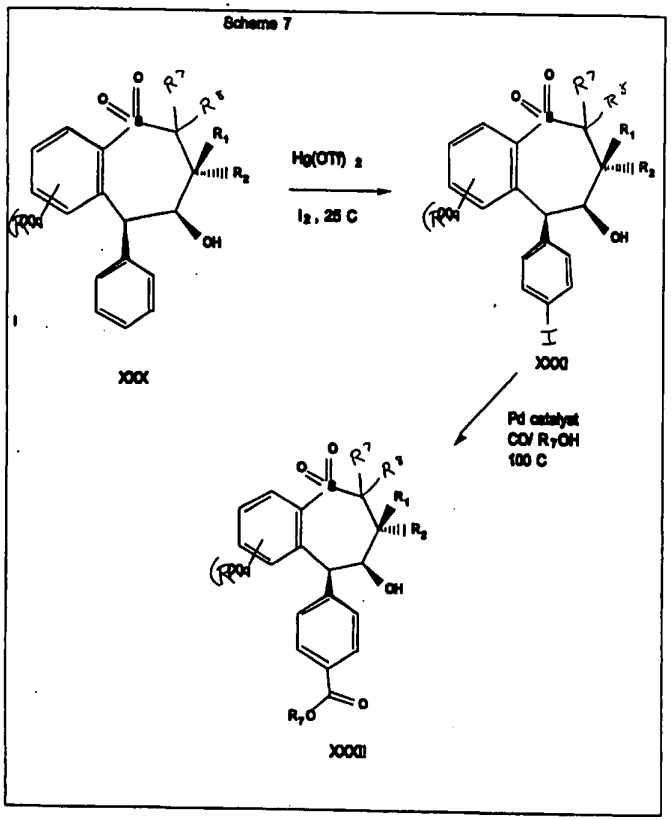


In Scheme 6, reduction of the sulfone-aldehyde XXV with hydrogen followed by reductive alkylation of the resulting amino derivative with hydrogen and an aldehyde catalyzed by palladium on carbon in the same reaction vessel yields the substituted amine derivative



XXVIII. Cyclization of XXVIII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention XXIXc and XXIXd.

Scheme 7 describes one of the methods of introducing a substituent to the aryl ring at the 5-position of benzothiepine. Iodination of 5-phenyl derivative XXX with iodine catalyzed by mercuric triflate gives the iodo derivative XXXI, which upon palladium-catalyzed carbonylation in an alcohol yields the carboxylate XXXII. Hydrolysis of the carboxylate



and derivatization of the resulting acid to acid derivatives are well known in the art.

Abbreviations used in the foregoing description have the following meanings:

THF---tetrahydrofuran

PTC---phase transfer catalyst

Aliquart 336---methyltricaprylylammonium chloride

MCPBA---m-chloroperbenzoic acid

Celite--- a brand of diatomaceous earth filtering aid

DMF---dimethylformamide

DME----ethylene glycol dimethyl ether

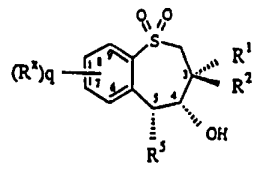
BOC---t-butoxycarbonyl group

R^1 and R^2 can be selected from among substituted and unsubstituted C_1 to C_{10} alkyl wherein the substituent(s) can be selected from among alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing heterocycles joined to the C_1 to C_{10} alkyl through an ether linkage. Substituents at the 3-carbon can include ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, $-CH_2C(=O)C_2H_5$, $-CH_2OC_2H_5$, and $-CH_2O-(4-picoline)$. Ethyl, n-propyl, n-butyl, and isobutyl are preferred. In certain particularly preferred compounds of the present invention, substituents R^1 and R^2 are identical, for example n-butyl/n-butyl, so that the compound is achiral at the 3-carbon. Eliminating optical isomerism at the 3-carbon simplifies the selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport inhibitor. In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R^5) on the benzo- ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl,

alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxy-carbonylalkyl amine, haloalkylthio, haloalkylsulfinyl, haloalkylsufonyl, amino, N-alkylamino, N,N-dialkylamino, (N)-alkoxycarbamoyl, (N)-aryloxycarbamoyl, (N)-aralkyloxycarbamoyl, trialkylammonium (especially with a halide counterion), (N)-amido, (N)-alkylamido, -N-alkylamido, -N,N-dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)-alkylsulfonamido, (N)-haloalkylsulfonamido, carboxyalkyl-amino, trialkylammonium salt, (N)-carbamic acid, alkyl or benzyl ester, N-acylamine, hydroxylamine, haloacylamine, carbohydrate, thiophene a trialkyl ammonium salt having a carboxylic acid or hydroxy substituent on one or more of the alkyl substituents, an alkylene bridge having a quaternary ammonium salt substituted thereon, $-[O(CH_2)_w]_x-X$ where x is 2 to 12, w is 2 or 3 and X is a halo or a quaternary ammonium salt, and (N)-nitrogen containing heterocycle wherein the nitrogen of said heterocycle is optionally quaternized. Among the preferred species which may constitute R^x are methyl, ethyl, isopropyl, t-butyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, bromo, fluoro, methylsulfinyl, methylsulfonyl, ethylthio, amino, hydroxylamine, N-methylamino, N,N-dimethylamino, N,N-diethylamino, (N)-benzyloxycarbamoyl, trimethylammonium, A^-, $-NHC(=O)CH_3$, $-NHC(=O)C_5H_{11}$, $-NHC(=O)C_6H_{13}$, carboxyethylamino, (N)-morpholinyl, (N)-azetidinyl, (N)-N-methylazetidinium A^-, (N)-pyrrolidinyl, pyrrolyl, (N)-N-methylpyridinium A^-, (N)-N-methylmorpholinium A^-, and N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)-

N-hexylamino, thiophene, $-N^+(CH_3)_2CO_2H\ I^-$, $-NCH_2CH_2CO_2H$, -(N)-N'-dimethylpiperazinium I^-, (N)-t-butyloxycarbamoyl, (N)-methylsulfonamido, (N)N'-methylpyrrolidinium, and $-(OCH_2CH_2)_2I$, where A^- is a pharmaceutically acceptable anion. The benzo ring is can be mono-substituted at the 6, 7 or 8 position, or disubstituted at the 7- and -8 positions. Also included are the 6,7,8-trialkoxy compounds, for example the 6,7,8-trimethoxy compounds. A variety of other substituents can be advantageously present on the 6, 7, 8, and/or 9- positions of the benzo ring, including, for example, guanidinyl, cycloalkyl, carbohydrate (e.g., a 5 or 6 carbon monosaccharide), peptide, and quaternary ammonium salts linked to the ring via poly(oxyalkylene) linkages, e.g., $-(OCH_2CH_2)_x-N^+R^{13}R^{14}R^{15}A^-$, where x is 2 to 10. Exemplary compounds are those set forth below in Table 1.

TABLE 1
Alternative compounds #3 (Family F101.xxx.yyy) *



Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)q$
F101.001	01	n-propyl	Ph-	7-methyl
	02	n-propyl	Ph-	7-ethyl
	03	n-propyl	Ph-	7-iso-propyl
	04	n-propyl	Ph-	7-tert-butyl
	05	n-propyl	Ph-	7-OH
	06	n-propyl	Ph-	7-OCH_3
	07	n-propyl	Ph-	7-O(iso-propyl)
	08	n-propyl	Ph-	7-SCH_3
	09	n-propyl	Ph-	7-$SOCH_3$
	10	n-propyl	Ph-	7-SO_2CH_3

* General Notes

In the description of the substituents "(N)" indicates that a nitrogen bearing substituent is bonded to the ring structure via the nitrogen atom.

Similarly, 2-thiophene indicates a bond in the 2 position of the thiophene ring. A similar convention is used for other heterocyclic substituents.

Abbreviations and Definitions

NH-CBZ is defined as $-HNC(=O)OCH_2Ph$

11	n-propyl	Ph-	7-SCH_2CH_3
12	n-propyl	Ph-	7-NH_2
13	n-propyl	Ph-	7-NHOH
14	n-propyl	Ph-	7-$NHCH_3$
15	n-propyl	Ph-	7-$N(CH_3)_2$
16	n-propyl	Ph-	7-$N^+(CH_3)_3$, I^-
17	n-propyl	Ph-	7-$NHC(=O)CH_3$
18	n-propyl	Ph-	7-$N(CH_2CH_3)_2$
19	n-propyl	Ph-	7-$NMeCH_2CO_2H$
20	n-propyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	n-propyl	Ph-	7-(N)-morpholine
22	n-propyl	Ph-	7-(N)-azetidine
23	n-propyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	n-propyl	Ph-	7-(N)-pyrrolidine
25	n-propyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	n-propyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	n-propyl	Ph-	7-(N)-N'-methylpiperazine
28	n-propyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	n-propyl	Ph-	7-NH-CBZ
30	n-propyl	Ph-	7-$NHC(O)C_5H_{11}$
31	n-propyl	Ph-	7-$NHC(O)CH_2Br$
32	n-propyl	Ph-	7-$NH-C(NH)NH_2$
33	n-propyl	Ph-	7-(2)-thiophene
34	n-propyl	Ph-	8-methyl
35	n-propyl	Ph-	8-ethyl
36	n-propyl	Ph-	8-iso-propyl
37	n-propyl	Ph-	8-tert-butyl
38	n-propyl	Ph-	8-OH
39	n-propyl	Ph-	8-OCH_3
40	n-propyl	Ph-	8-O(iso-propyl)
41	n-propyl	Ph-	8-SCH_3
42	n-propyl	Ph-	8-$SOCH_3$
43	n-propyl	Ph-	8-SO_2CH_3
44	n-propyl	Ph-	8-SCH_2CH_3
45	n-propyl	Ph-	8-NH_2
46	n-propyl	Ph-	8-NHOH
47	n-propyl	Ph-	8-$NHCH_3$
48	n-propyl	Ph-	8-$N(CH_3)_2$
49	n-propyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-propyl	Ph-	8-$NHC(=O)CH_3$
51	n-propyl	Ph-	8-$N(CH_2CH_3)_2$
52	n-propyl	Ph-	8-$NMeCH_2CO_2H$

53	n-propyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-propyl	Ph-	8-(N)-morpholine
55	n-propyl	Ph-	8-(N)-azetidine
56	n-propyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-propyl	Ph-	8-(N)-pyrrolidine
58	n-propyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-propyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-propyl	Ph-	8-(N)-N'-methylpiperazine
61	n-propyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	n-propyl	Ph-	8-NH-CBz
63	n-propyl	Ph-	8-$NHC(O)C_5H_{11}$
64	n-propyl	Ph-	8-$NHC(O)CH_2Br$
65	n-propyl	Ph-	8-$NH-C(NH)NH_2$
66	n-propyl	Ph-	8-(2)-thiophene
67	n-propyl	Ph-	9-methyl
68	n-propyl	Ph-	9-ethyl
69	n-propyl	Ph-	9-iso-propyl
70	n-propyl	Ph-	9-tert-butyl
71	n-propyl	Ph-	9-OH
72	n-propyl	Ph-	9-OCH_3
73	n-propyl	Ph-	9-O(iso-propyl)
74	n-propyl	Ph-	9-SCH_3
75	n-propyl	Ph-	9-$SOCH_3$
76	n-propyl	Ph-	9-SO_2CH_3
77	n-propyl	Ph-	9-SCH_2CH_3
78	n-propyl	Ph-	9-NH_2
79	n-propyl	Ph-	9-NHOH
80	n-propyl	Ph-	9-$NHCH_3$
81	n-propyl	Ph-	9-$N(CH_3)_2$
82	n-propyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	n-propyl	Ph-	9-NHC(=O)CH_3
84	n-propyl	Ph-	9-$N(CH_2CH_3)_2$
85	n-propyl	Ph-	9-$NMeCH_2CO_2H$
86	n-propyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	n-propyl	Ph-	9-(N)-morpholine
88	n-propyl	Ph-	9-(N)-azetidine
89	n-propyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	n-propyl	Ph-	9-(N)-pyrrolidine
91	n-propyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	n-propyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	n-propyl	Ph-	9-(N)-N'-methylpiperazine
93	n-propyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	n-propyl	Ph-	9-NH-CBz

96	n-propyl	Ph-	9-$NHC(O)C_5H_{11}$
97	n-propyl	Ph-	9-$NHC(O)CH_2Br$
98	n-propyl	Ph-	9-$NH-C(NH)NH_2$
99	n-propyl	Ph-	9-(2)-thiophene
100	n-propyl	Ph-	7-OCH_3, 8-OCH_3
101	n-propyl	Ph-	7-SCH_3, 8-OCH_3
102	n-propyl	Ph-	7-SCH_3, 8-SCH_3
103	n-propyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.002	01	n-butyl	Ph-	7-methyl
	02	n-butyl	Ph-	7-ethyl
	03	n-butyl	Ph-	7-iso-propyl
	04	n-butyl	Ph-	7-tert-butyl
	05	n-butyl	Ph-	7-OH
	06	n-butyl	Ph-	7-OCH_3
	07	n-butyl	Ph-	7-O(iso-propyl)
	08	n-butyl	Ph-	7-SCH_3
	09	n-butyl	Ph-	7-$SOCH_3$
	10	n-butyl	Ph-	7-SO_2CH_3
	11	n-butyl	Ph-	7-SCH_2CH_3
	12	n-butyl	Ph-	7-NH_2
	13	n-butyl	Ph-	7-NHOH
	14	n-butyl	Ph-	7-$NHCH_3$
	15	n-butyl	Ph-	7-$N(CH_3)_2$
	16	n-butyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	n-butyl	Ph-	7-NHC(=O)CH_3
	18	n-butyl	Ph-	7-$N(CH_2CH_3)_2$
	19	n-butyl	Ph-	7-$NMeCH_2CO_2H$
	20	n-butyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	n-butyl	Ph-	7-(N)-morpholine
	22	n-butyl	Ph-	7-(N)-azetidine
	23	n-butyl	Ph-	7-(N)-N-methylazetidinium, I^-
	24	n-butyl	Ph-	7-(N)-pyrrolidine
	25	n-butyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	n-butyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	n-butyl	Ph-	7-(N)-N'-methylpiperazine
	28	n-butyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	n-butyl	Ph-	7-NH-CBz
	30	n-butyl	Ph-	7-$NHC(O)C_5H_{11}$
	31	n-butyl	Ph-	7-$NHC(O)CH_2Br$

32	n-butyl	Ph-	7-NH-C(NH)NH_2
33	n-butyl	Ph-	7-(2)-thiophene
34	n-butyl	Ph-	8-methyl
35	n-butyl	Ph-	8-ethyl
36	n-butyl	Ph-	8-iso-propyl
37	n-butyl	Ph-	8-tert-butyl
38	n-butyl	Ph-	8-OH
39	n-butyl	Ph-	8-OCH_3
40	n-butyl	Ph-	8-O(iso-propyl)
41	n-butyl	Ph-	8-SCH_3
42	n-butyl	Ph-	8-$SOCH_3$
43	n-butyl	Ph-	8-SO_2CH_3
44	n-butyl	Ph-	8-SCH_2CH_3
45	n-butyl	Ph-	8-NH_2
46	n-butyl	Ph-	8-NHOH
47	n-butyl	Ph-	8-$NHCH_3$
48	n-butyl	Ph-	8-$N(CH_3)_2$
49	n-butyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-butyl	Ph-	8-$NHC(=O)CH_3$
51	n-butyl	Ph-	8-$N(CH_2CH_3)_2$
52	n-butyl	Ph-	8-$NMeCH_2CO_2H$
53	n-butyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-butyl	Ph-	8-(N)-morpholine
55	n-butyl	Ph-	8-(N)-azetidine
56	n-butyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-butyl	Ph-	8-(N)-pyrrolidine
58	n-butyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-butyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-butyl	Ph-	8-(N)-N'-methylpiperazine
61	n-butyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	n-butyl	Ph-	8-NH-CBZ
63	n-butyl	Ph-	8-$NHC(O)C_5H_{11}$
64	n-butyl	Ph-	8-$NHC(O)CH_2Br$
65	n-butyl	Ph-	8-NH-C(NH)NH_2
66	n-butyl	Ph-	8-(2)-thiophene
67	n-butyl	Ph-	9-methyl
68	n-butyl	Ph-	9-ethyl
69	n-butyl	Ph-	9-iso-propyl
70	n-butyl	Ph-	9-tert-butyl
71	n-butyl	Ph-	9-OH
72	n-butyl	Ph-	9-OCH_3
73	n-butyl	Ph-	9-O(iso-propyl)

74	n-butyl	Ph-	9-SCH_3
75	n-butyl	Ph-	9-$SOCH_3$
76	n-butyl	Ph-	9-SO_2CH_3
77	n-butyl	Ph-	9-SCH_2CH_3
78	n-butyl	Ph-	9-NH_2
79	n-butyl	Ph-	9-NHOH
80	n-butyl	Ph-	9-$NHCH_3$
81	n-butyl	Ph-	9-$N(CH_3)_2$
82	n-butyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	n-butyl	Ph-	9-$NHC(=O)CH_3$
84	n-butyl	Ph-	9-$N(CH_2CH_3)_2$
85	n-butyl	Ph-	9-$NMeCH_2CO_2H$
86	n-butyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	n-butyl	Ph-	9-(N)-morpholine
88	n-butyl	Ph-	9-(N)-azetidine
89	n-butyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	n-butyl	Ph-	9-(N)-pyrrolidine
91	n-butyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	n-butyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	n-butyl	Ph-	9-(N)-N'-methylpiperazine
93	n-butyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	n-butyl	Ph-	9-NH-CBZ
96	n-butyl	Ph-	9-$NHC(O)C_5H_{11}$
97	n-butyl	Ph-	9-$NHC(O)CH_2Br$
98	n-butyl	Ph-	9-NH-C(NH)NH_2
99	n-butyl	Ph-	9-(2)-thiophene
100	n-butyl	Ph-	7-OCH_3, 8-OCH_3
101	n-butyl	Ph-	7-SCH_3, 8-OCH_3
102	n-butyl	Ph-	7-SCH_3, 8-SCH_3
103	n-butyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FTF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.003	01	n-pentyl	Ph-	7-methyl
	02	n-pentyl	Ph-	7-ethyl
	03	n-pentyl	Ph-	7-iso-propyl
	04	n-pentyl	Ph-	7-tert-butyl
	05	n-pentyl	Ph-	7-OH
	06	n-pentyl	Ph-	7-OCH_3
	07	n-pentyl	Ph-	7-O(iso-propyl)
	08	n-pentyl	Ph-	7-SCH_3
	09	n-pentyl	Ph-	7-$SOCH_3$

10	n-pentyl	Ph-	7-SO_2CH_3
11	n-pentyl	Ph-	7-SCH_2CH_3
12	n-pentyl	Ph-	7-NH_2
13	n-pentyl	Ph-	7-NHOH
14	n-pentyl	Ph-	7-$NHCH_3$
15	n-pentyl	Ph-	7-$N(CH_3)_2$
16	n-pentyl	Ph-	7-$N^+(CH_3)_3$, I^-
17	n-pentyl	Ph-	7-$NHC(=O)CH_3$
18	n-pentyl	Ph-	7-$N(CH_2CH_3)_2$
19	n-pentyl	Ph-	7-$NMeCH_2CO_2H$
20	n-pentyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	n-pentyl	Ph-	7-(N)-morpholine
22	n-pentyl	Ph-	7-(N)-azetidine
23	n-pentyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	n-pentyl	Ph-	7-(N)-pyrrolidine
25	n-pentyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	n-pentyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	n-pentyl	Ph-	7-(N)-N'-methylpiperazine
28	n-pentyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	n-pentyl	Ph-	7-NH-CBZ
30	n-pentyl	Ph-	7-$NHC(O)C_5H_{11}$
31	n-pentyl	Ph-	7-$NHC(O)CH_2Br$
32	n-pentyl	Ph-	7-$NH-C(NH)NH_2$
33	n-pentyl	Ph-	7-(2)-thiophene
34	n-pentyl	Ph-	8-methyl
35	n-pentyl	Ph-	8-ethyl
36	n-pentyl	Ph-	8-iso-propyl
37	n-pentyl	Ph-	8-tert-butyl
38	n-pentyl	Ph-	8-OH
39	n-pentyl	Ph-	8-OCH_3
40	n-pentyl	Ph-	8-O(iso-propyl)
41	n-pentyl	Ph-	8-SCH_3
42	n-pentyl	Ph-	8-$SOCH_3$
43	n-pentyl	Ph-	8-SO_2CH_3
44	n-pentyl	Ph-	8-SCH_2CH_3
45	n-pentyl	Ph-	8-NH_2
46	n-pentyl	Ph-	8-NHOH
47	n-pentyl	Ph-	8-$NHCH_3$
48	n-pentyl	Ph-	8-$N(CH_3)_2$
49	n-pentyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-pentyl	Ph-	8-$NHC(=O)CH_3$
51	n-pentyl	Ph-	8-$N(CH_2CH_3)_2$

52	n-pentyl	Ph-	8-$NMeCH_2CO_2H$
53	n-pentyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-pentyl	Ph-	8-(N)-morpholine
55	n-pentyl	Ph-	8-(N)-azetidine
56	n-pentyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-pentyl	Ph-	8-(N)-pyrrolidine
58	n-pentyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-pentyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-pentyl	Ph-	8-(N)-N'-methylpiperazine
61	n-pentyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	n-pentyl	Ph-	8-NH-CBZ
63	n-pentyl	Ph-	8-$NHC(O)C_5H_{11}$
64	n-pentyl	Ph-	8-$NHC(O)CH_2Br$
65	n-pentyl	Ph-	8-$NH-C(NH)NH_2$
66	n-pentyl	Ph-	8-(2)-thiophene
67	n-pentyl	Ph-	9-methyl
68	n-pentyl	Ph-	9-ethyl
69	n-pentyl	Ph-	9-iso-propyl
70	n-pentyl	Ph-	9-tert-butyl
71	n-pentyl	Ph-	9-OH
72	n-pentyl	Ph-	9-OCH_3
73	n-pentyl	Ph-	9-O(iso-propyl)
74	n-pentyl	Ph-	9-SCH_3
75	n-pentyl	Ph-	9-$SOCH_3$
76	n-pentyl	Ph-	9-SO_2CH_3
77	n-pentyl	Ph-	9-SCH_2CH_3
78	n-pentyl	Ph-	9-NH_2
79	n-pentyl	Ph-	9-NHOH
80	n-pentyl	Ph-	9-$NHCH_3$
81	n-pentyl	Ph-	9-$N(CH_3)_2$
82	n-pentyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	n-pentyl	Ph-	9-$NHC(=O)CH_3$
84	n-pentyl	Ph-	9-$N(CH_2CH_3)_2$
85	n-pentyl	Ph-	9-$NMeCH_2CO_2H$
86	n-pentyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	n-pentyl	Ph-	9-(N)-morpholine
88	n-pentyl	Ph-	9-(N)-azetidine
89	n-pentyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	n-pentyl	Ph-	9-(N)-pyrrolidine
91	n-pentyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	n-pentyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	n-pentyl	Ph-	9-(N)-N'-methylpiperazine
93	n-pentyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-

95	n-pentyl	Ph-	9-NH-CBZ
96	n-pentyl	Ph-	9-NHC(O)C_5H_{11}
97	n-pentyl	Ph-	9-NHC(O)CH_2Br
98	n-pentyl	Ph-	9-NH-C(NH)NH_2
99	n-pentyl	Ph-	9-(2)-thiophene
100	n-pentyl	Ph-	7-OCH_3, 8-OCH_3
101	n-pentyl	Ph-	7-SCH_3, 8-OCH_3
102	n-pentyl	Ph-	7-SCH_3, 8-SCH_3
103	n-pentyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FPT,xxx,	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.004	01	n-hexyl	Ph-	7-methyl
	02	n-hexyl	Ph-	7-ethyl
	03	n-hexyl	Ph-	7-iso-propyl
	04	n-hexyl	Ph-	7-tert-butyl
	05	n-hexyl	Ph-	7-OH
	06	n-hexyl	Ph-	7-OCH_3
	07	n-hexyl	Ph-	7-O(iso-propyl)
	08	n-hexyl	Ph-	7-SCH_3
	09	n-hexyl	Ph-	7-$SOCH_3$
	10	n-hexyl	Ph-	7-SO_2CH_3
	11	n-hexyl	Ph-	7-SCH_2CH_3
	12	n-hexyl	Ph-	7-NH_2
	13	n-hexyl	Ph-	7-NHOH
	14	n-hexyl	Ph-	7-$NHCH_3$
	15	n-hexyl	Ph-	7-$N(CH_3)_2$
	16	n-hexyl	Ph-	7-$N^+(CH_3)_3$, I^-
	17	n-hexyl	Ph-	7-NHC(=O)CH_3
	18	n-hexyl	Ph-	7-$N(CH_2CH_3)_2$
	19	n-hexyl	Ph-	7-$NMeCH_2CO_2H$
	20	n-hexyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	n-hexyl	Ph-	7-(N)-morpholine
	22	n-hexyl	Ph-	7-(N)-azetidine
	23	n-hexyl	Ph-	7-(N)-N-methylazetidinium, I^-
	24	n-hexyl	Ph-	7-(N)-pyrrolidine
	25	n-hexyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	n-hexyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	n-hexyl	Ph-	7-(N)-N'-methylpiperazine
	28	n-hexyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	n-hexyl	Ph-	7-NH-CBZ
	30	n-hexyl	Ph-	7-NHC(O)C_5H_{11}

31	n-hexyl	Ph-	7-NHC(O)CH_2Br
32	n-hexyl	Ph-	7-NH-C(NH)NH_2
33	n-hexyl	Ph-	7-(2)-thiophene
34	n-hexyl	Ph-	8-methyl
35	n-hexyl	Ph-	8-ethyl
36	n-hexyl	Ph-	8-iso-propyl
37	n-hexyl	Ph-	8-tert-butyl
38	n-hexyl	Ph-	8-OH
39	n-hexyl	Ph-	8-OCH_3
40	n-hexyl	Ph-	8-O(iso-propyl)
41	n-hexyl	Ph-	8-SCH_3
42	n-hexyl	Ph-	8-$SOCH_3$
43	n-hexyl	Ph-	8-SO_2CH_3
44	n-hexyl	Ph-	8-SCH_2CH_3
45	n-hexyl	Ph-	8-NH_2
46	n-hexyl	Ph-	8-NHOH
47	n-hexyl	Ph-	8-$NHCH_3$
48	n-hexyl	Ph-	8-$N(CH_3)_2$
49	n-hexyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	n-hexyl	Ph-	8-NHC(=O)CH_3
51	n-hexyl	Ph-	8-$N(CH_2CH_3)_2$
52	n-hexyl	Ph-	8-$NMeCH_2CO_2H$
53	n-hexyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	n-hexyl	Ph-	8-(N)-morpholine
55	n-hexyl	Ph-	8-(N)-azetidine
56	n-hexyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	n-hexyl	Ph-	8-(N)-pyrrolidine
58	n-hexyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	n-hexyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	n-hexyl	Ph-	8-(N)-N'-methylpiperazine
61	n-hexyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	n-hexyl	Ph-	8-NH-CBZ
63	n-hexyl	Ph-	8-NHC(O)C_5H_{11}
64	n-hexyl	Ph-	8-NHC(O)CH_2Br
65	n-hexyl	Ph-	8-NH-C(NH)NH_2
66	n-hexyl	Ph-	8-(2)-thiophene
67	n-hexyl	Ph-	9-methyl
68	n-hexyl	Ph-	9-ethyl
69	n-hexyl	Ph-	9-iso-propyl
70	n-hexyl	Ph-	9-tert-butyl
71	n-hexyl	Ph-	9-OH
72	n-hexyl	Ph-	9-OCH_3

73	n-hexyl	Ph-	9-O(iso-propyl)
74	n-hexyl	Ph-	9-SCH_3
75	n-hexyl	Ph-	9-$SOCH_3$
76	n-hexyl	Ph-	9-SO_2CH_3
77	n-hexyl	Ph-	9-SCH_2CH_3
78	n-hexyl	Ph-	9-NH_2
79	n-hexyl	Ph-	9-NHOH
80	n-hexyl	Ph-	9-$NHCH_3$
81	n-hexyl	Ph-	9-$N(CH_3)_2$
82	n-hexyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	n-hexyl	Ph-	9-$NHC(=O)CH_3$
84	n-hexyl	Ph-	9-$N(CH_2CH_3)_2$
85	n-hexyl	Ph-	9-$NMeCH_2CO_2H$
86	n-hexyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	n-hexyl	Ph-	9-(N)-morpholine
88	n-hexyl	Ph-	9-(N)-azetidine
89	n-hexyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	n-hexyl	Ph-	9-(N)-pyrrolidine
91	n-hexyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	n-hexyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	n-hexyl	Ph-	9-(N)-N'-methylpiperazine
93	n-hexyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	n-hexyl	Ph-	9-NH-CBZ
96	n-hexyl	Ph-	9-$NHC(O)C_5H_{11}$
97	n-hexyl	Ph-	9-$NHC(O)CH_2Br$
98	n-hexyl	Ph-	9-$NH-C(NH)NH_2$
99	n-hexyl	Ph-	9-(2)-thiophene
100	n-hexyl	Ph-	7-OCH_3, 8-OCH_3
101	n-hexyl	Ph-	7-SCH_3, 8-OCH_3
102	n-hexyl	Ph-	7-SCH_3, 8-SCH_3
103	n-hexyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.005	01	iso-propyl	Ph-	7-methyl
	02	iso-propyl	Ph-	7-ethyl
	03	iso-propyl	Ph-	7-iso-propyl
	04	iso-propyl	Ph-	7-tert-butyl
	05	iso-propyl	Ph-	7-OH
	06	iso-propyl	Ph-	7-OCH_3
	07	iso-propyl	Ph-	7-O(iso-propyl)
	08	iso-propyl	Ph-	7-SCH_3

09	iso-propyl	Ph-	7-$SOCH_3$
10	iso-propyl	Ph-	7-SO_2CH_3
11	iso-propyl	Ph-	7-SCH_2CH_3
12	iso-propyl	Ph-	7-NH_2
13	iso-propyl	Ph-	7-NHOH
14	iso-propyl	Ph-	7-$NHCH_3$
15	iso-propyl	Ph-	7-$N(CH_3)_2$
16	iso-propyl	Ph-	7-$N^+(CH_3)_3$, I^-
17	iso-propyl	Ph-	7-$NHC(=O)CH_3$
18	iso-propyl	Ph-	7-$N(CH_2CH_3)_2$
19	iso-propyl	Ph-	7-$NMeCH_2CO_2H$
20	iso-propyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	iso-propyl	Ph-	7-(N)-morpholine
22	iso-propyl	Ph-	7-(N)-azetidine
23	iso-propyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	iso-propyl	Ph-	7-(N)-pyrrolidine
25	iso-propyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	iso-propyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	iso-propyl	Ph-	7-(N)-N'-methylpiperazine
28	iso-propyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	iso-propyl	Ph-	7-NH-CBZ
30	iso-propyl	Ph-	7-$NHC(O)C_5H_{11}$
31	iso-propyl	Ph-	7-$NHC(O)CH_2Br$
32	iso-propyl	Ph-	7-$NH-C(NH)NH_2$
33	iso-propyl	Ph-	7-(2)-thiophene
34	iso-propyl	Ph-	8-methyl
35	iso-propyl	Ph-	8-ethyl
36	iso-propyl	Ph-	8-iso-propyl
37	iso-propyl	Ph-	8-tert-butyl
38	iso-propyl	Ph-	8-OH
39	iso-propyl	Ph-	8-OCH_3
40	iso-propyl	Ph-	8-O(iso-propyl)
41	iso-propyl	Ph-	8-SCH_3
42	iso-propyl	Ph-	8-$SOCH_3$
43	iso-propyl	Ph-	8-SO_2CH_3
44	iso-propyl	Ph-	8-SCH_2CH_3
45	iso-propyl	Ph-	8-NH_2
46	iso-propyl	Ph-	8-NHOH
47	iso-propyl	Ph-	8-$NHCH_3$
48	iso-propyl	Ph-	8-$N(CH_3)_2$
49	iso-propyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	iso-propyl	Ph-	8-$NHC(=O)CH_3$

51	iso-propyl	Ph-	8-N(CH$_2$CH$_3$)$_2$
52	iso-propyl	Ph-	8-NMeCH$_2$CO$_2$H
53	iso-propyl	Ph-	8-N$^+$(Me)$_2$CH$_2$CO$_2$H, I$^-$
54	iso-propyl	Ph-	8-(N)-morpholine
55	iso-propyl	Ph-	8-(N)-azetidine
56	iso-propyl	Ph-	8-(N)-N-methylazetidinium, I$^-$
57	iso-propyl	Ph-	8-(N)-pyrrolidine
58	iso-propyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I$^-$
59	iso-propyl	Ph-	8-(N)-N-methyl-morpholinium, I$^-$
60	iso-propyl	Ph-	8-(N)-N'-methylpiperazine
61	iso-propyl	Ph-	8-(N)-N'-dimethylpiperazinium, I$^-$
62	iso-propyl	Ph-	8-NH-CBZ
63	iso-propyl	Ph-	8-NHC(O)C$_5$H$_{11}$
64	iso-propyl	Ph-	8-NHC(O)CH$_2$Br
65	iso-propyl	Ph-	8-NH-C(NH)NH$_2$
66	iso-propyl	Ph-	8-(2)-thiophene
67	iso-propyl	Ph-	9-methyl
68	iso-propyl	Ph-	9-ethyl
69	iso-propyl	Ph-	9-iso-propyl
70	iso-propyl	Ph-	9-tert-butyl
71	iso-propyl	Ph-	9-OH
72	iso-propyl	Ph-	9-OCH$_3$
73	iso-propyl	Ph-	9-O(iso-propyl)
74	iso-propyl	Ph-	9-SCH$_3$
75	iso-propyl	Ph-	9-SOCH$_3$
76	iso-propyl	Ph-	9-SO$_2$CH$_3$
77	iso-propyl	Ph-	9-SCH$_2$CH$_3$
78	iso-propyl	Ph-	9-NH$_2$
79	iso-propyl	Ph-	9-NHOH
80	iso-propyl	Ph-	9-NHCH$_3$
81	iso-propyl	Ph-	9-N(CH$_3$)$_2$
82	iso-propyl	Ph-	9-N$^+$(CH$_3$)$_3$, I$^-$
83	iso-propyl	Ph-	9-NHC(=O)CH$_3$
84	iso-propyl	Ph-	9-N(CH$_2$CH$_3$)$_2$
85	iso-propyl	Ph-	9-NMeCH$_2$CO$_2$H
86	iso-propyl	Ph-	9-N$^+$(Me)$_2$CH$_2$CO$_2$H, I$^-$
87	iso-propyl	Ph-	9-(N)-morpholine
88	iso-propyl	Ph-	9-(N)-azetidine
89	iso-propyl	Ph-	9-(N)-N-methylazetidinium, I$^-$
90	iso-propyl	Ph-	9-(N)-pyrrolidine
91	iso-propyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I$^-$
92	iso-propyl	Ph-	9-(N)-N-methyl-morpholinium, I$^-$
93	iso-propyl	Ph-	9-(N)-N'-methylpiperazine

93	iso-propyl	Ph-	9-(N)-N'-dimethylpiperazinium, I$^-$
95	iso-propyl	Ph-	9-NH-CBZ
96	iso-propyl	Ph-	9-NHC(O)C$_5$H$_{11}$
97	iso-propyl	Ph-	9-NHC(O)CH$_2$Br
98	iso-propyl	Ph-	9-NH-C(NH)NH$_2$
99	iso-propyl	Ph-	9-(2)-thiophene
100	iso-propyl	Ph-	7-OCH$_3$, 8-OCH$_3$
101	iso-propyl	Ph-	7-SCH$_3$, 8-OCH$_3$
102	iso-propyl	Ph-	7-SCH$_3$, 8-SCH$_3$
103	iso-propyl	Ph-	6-OCH$_3$, 7-OCH$_3$, 8-OCH$_3$

Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	(R^x)q
F101.006	01	iso-butyl	Ph-	7-methyl
	02	iso-butyl	Ph-	7-ethyl
	03	iso-butyl	Ph-	7-iso-propyl
	04	iso-butyl	Ph-	7-tert-butyl
	05	iso-butyl	Ph-	7-OH
	06	iso-butyl	Ph-	7-OCH$_3$
	07	iso-butyl	Ph-	7-O(iso-propyl)
	08	iso-butyl	Ph-	7-SCH$_3$
	09	iso-butyl	Ph-	7-SOCH$_3$
	10	iso-butyl	Ph-	7-SO$_2$CH$_3$
	11	iso-butyl	Ph-	7-SCH$_2$CH$_3$
	12	iso-butyl	Ph-	7-NH$_2$
	13	iso-butyl	Ph-	7-NHOH
	14	iso-butyl	Ph-	7-NHCH$_3$
	15	iso-butyl	Ph-	7-N(CH$_3$)$_2$
	16	iso-butyl	Ph-	7-N$^+$(CH$_3$)$_3$, I$^-$
	17	iso-butyl	Ph-	7-NHC(=O)CH$_3$
	18	iso-butyl	Ph-	7-N(CH$_2$CH$_3$)$_2$
	19	iso-butyl	Ph-	7-NMeCH$_2$CO$_2$H
	20	iso-butyl	Ph-	7-N$^+$(Me)$_2$CH$_2$CO$_2$H, I$^-$
	21	iso-butyl	Ph-	7-(N)-morpholine
	22	iso-butyl	Ph-	7-(N)-azetidine
	23	iso-butyl	Ph-	7-(N)-N-methylazetidinium, I$^-$
	24	iso-butyl	Ph-	7-(N)-pyrrolidine
	25	iso-butyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I$^-$
	26	iso-butyl	Ph-	7-(N)-N-methyl-morpholinium, I$^-$
	27	iso-butyl	Ph-	7-(N)-N'-methylpiperazine
	28	iso-butyl	Ph-	7-(N)-N'-dimethylpiperazinium, I$^-$
	29	iso-butyl	Ph-	7-NH-CBZ

30	iso-butyl	Ph-	7-NHC(O)C_5H_{11}
31	iso-butyl	Ph-	7-NHC(O)CH_2Br
32	iso-butyl	Ph-	7-NH-C(NH)NH_2
33	iso-butyl	Ph-	7-(2)-thiophene
34	iso-butyl	Ph-	8-methyl
35	iso-butyl	Ph-	8-ethyl
36	iso-butyl	Ph-	8-iso-propyl
37	iso-butyl	Ph-	8-tert-butyl
38	iso-butyl	Ph-	8-OH
39	iso-butyl	Ph-	8-OCH_3
40	iso-butyl	Ph-	8-O(iso-propyl)
41	iso-butyl	Ph-	8-SCH_3
42	iso-butyl	Ph-	8-$SOCH_3$
43	iso-butyl	Ph-	8-SO_2CH_3
44	iso-butyl	Ph-	8-SCH_2CH_3
45	iso-butyl	Ph-	8-NH_2
46	iso-butyl	Ph-	8-NHOH
47	iso-butyl	Ph-	8-$NHCH_3$
48	iso-butyl	Ph-	8-$N(CH_3)_2$
49	iso-butyl	Ph-	8-$N^+(CH_3)_3$, I^-
50	iso-butyl	Ph-	8-NHC(=O)CH_3
51	iso-butyl	Ph-	8-$N(CH_2CH_3)_2$
52	iso-butyl	Ph-	8-$NMeCH_2CO_2H$
53	iso-butyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	iso-butyl	Ph-	8-(N)-morpholine
55	iso-butyl	Ph-	8-(N)-azetidine
56	iso-butyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	iso-butyl	Ph-	8-(N)-pyrrolidine
58	iso-butyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	iso-butyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	iso-butyl	Ph-	8-(N)-N'-methylpiperazine
61	iso-butyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	iso-butyl	Ph-	8-NH-CBZ
63	iso-butyl	Ph-	8-NHC(O)C_5H_{11}
64	iso-butyl	Ph-	8-NHC(O)CH_2Br
65	iso-butyl	Ph-	8-NH-C(NH)NH_2
66	iso-butyl	Ph-	8-(2)-thiophene
67	iso-butyl	Ph-	9-methyl
68	iso-butyl	Ph-	9-ethyl
69	iso-butyl	Ph-	9-iso-propyl
70	iso-butyl	Ph-	9-tert-butyl
71	iso-butyl	Ph-	9-OH

72	iso-butyl	Ph-	9-OCH_3
73	iso-butyl	Ph-	9-O(iso-propyl)
74	iso-butyl	Ph-	9-SCH_3
75	iso-butyl	Ph-	9-$SOCH_3$
76	iso-butyl	Ph-	9-SO_2CH_3
77	iso-butyl	Ph-	9-SCH_2CH_3
78	iso-butyl	Ph-	9-NH_2
79	iso-butyl	Ph-	9-NHOH
80	iso-butyl	Ph-	9-$NHCH_3$
81	iso-butyl	Ph-	9-$N(CH_3)_2$
82	iso-butyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	iso-butyl	Ph-	9-NHC(=O)CH_3
84	iso-butyl	Ph-	9-$N(CH_2CH_3)_2$
85	iso-butyl	Ph-	9-$NMeCH_2CO_2H$
86	iso-butyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	iso-butyl	Ph-	9-(N)-morpholine
88	iso-butyl	Ph-	9-(N)-azetidine
89	iso-butyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	iso-butyl	Ph-	9-(N)-pyrrolidine
91	iso-butyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	iso-butyl	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	iso-butyl	Ph-	9-(N)-N'-methylpiperazine
93	iso-butyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	iso-butyl	Ph-	9-NH-CBZ
96	iso-butyl	Ph-	9-NHC(O)C_5H_{11}
97	iso-butyl	Ph-	9-NHC(O)CH_2Br
98	iso-butyl	Ph-	9-NH-C(NH)NH_2
99	iso-butyl	Ph-	9-(2)-thiophene
100	iso-butyl	Ph-	7-OCH_3, 8-OCH_3
101	iso-butyl	Ph-	7-SCH_3, 8-OCH_3
102	iso-butyl	Ph-	7-SCH_3, 8-SCH_3
103	iso-butyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.007	01	iso-pentyl	Ph-	7-methyl
	02	iso-pentyl	Ph-	7-ethyl
	03	iso-pentyl	Ph-	7-iso-propyl
	04	iso-pentyl	Ph-	7-tert-butyl
	05	iso-pentyl	Ph-	7-OH
	06	iso-pentyl	Ph-	7-OCH_3
	07	iso-pentyl	Ph-	7-O(iso-propyl)

08	iso-pentyl	Ph-	7-SCH_3
09	iso-pentyl	Ph-	7-$SOCH_3$
10	iso-pentyl	Ph-	7-SO_2CH_3
11	iso-pentyl	Ph-	7-SCH_2CH_3
12	iso-pentyl	Ph-	7-NH_2
13	iso-pentyl	Ph-	7-NHOH
14	iso-pentyl	Ph-	7-$NHCH_3$
15	iso-pentyl	Ph-	7-$N(CH_3)_2$
16	iso-pentyl	Ph-	7-$N^+(CH_3)_3$, I^-
17	iso-pentyl	Ph-	7-$NHC(=O)CH_3$
18	iso-pentyl	Ph-	7-$N(CH_2CH_3)_2$
19	iso-pentyl	Ph-	7-$NMeCH_2CO_2H$
20	iso-pentyl	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	iso-pentyl	Ph-	7-(N)-morpholine
22	iso-pentyl	Ph-	7-(N)-azetidine
23	iso-pentyl	Ph-	7-(N)-N-methylazetidinium, I^-
24	iso-pentyl	Ph-	7-(N)-pyrrolidine
25	iso-pentyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	iso-pentyl	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	iso-pentyl	Ph-	7-(N)-N'-methylpiperazine
28	iso-pentyl	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	iso-pentyl	Ph-	7-NH-CBz
30	iso-pentyl	Ph-	7-$NHC(O)C_5H_{11}$
31	iso-pentyl	Ph-	7-$NHC(O)CH_2Br$
32	iso-pentyl	Ph-	7-$NH-C(NH)NH_2$
33	iso-pentyl	Ph-	7-(2)-thiophene
34	iso-pentyl	Ph-	8-methyl
35	iso-pentyl	Ph-	8-ethyl
36	iso-pentyl	Ph-	8-iso-propyl
37	iso-pentyl	Ph-	8-tert-butyl
38	iso-pentyl	Ph-	8-OH
39	iso-pentyl	Ph-	8-OCH_3
40	iso-pentyl	Ph-	8-O(iso-propyl)
41	iso-pentyl	Ph-	8-SCH_3
42	iso-pentyl	Ph-	8-$SOCH_3$
43	iso-pentyl	Ph-	8-SO_2CH_3
44	iso-pentyl	Ph-	8-SCH_2CH_3
45	iso-pentyl	Ph-	8-NH_2
46	iso-pentyl	Ph-	8-NHOH
47	iso-pentyl	Ph-	8-$NHCH_3$
48	iso-pentyl	Ph-	8-$N(CH_3)_2$
49	iso-pentyl	Ph-	8-$N^+(CH_3)_3$, I^-

50	iso-pentyl	Ph-	8-$NHC(=O)CH_3$
51	iso-pentyl	Ph-	8-$N(CH_2CH_3)_2$
52	iso-pentyl	Ph-	8-$NMeCH_2CO_2H$
53	iso-pentyl	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	iso-pentyl	Ph-	8-(N)-morpholine
55	iso-pentyl	Ph-	8-(N)-azetidino
56	iso-pentyl	Ph-	8-(N)-N-methylazetidinium, I^-
57	iso-pentyl	Ph-	8-(N)-pyrrolidine
58	iso-pentyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	iso-pentyl	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	iso-pentyl	Ph-	8-(N)-N'-methylpiperazine
61	iso-pentyl	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	iso-pentyl	Ph-	8-NH-CBz
63	iso-pentyl	Ph-	8-$NHC(O)C_5H_{11}$
64	iso-pentyl	Ph-	8-$NHC(O)CH_2Br$
65	iso-pentyl	Ph-	8-$NH-C(NH)NH_2$
66	iso-pentyl	Ph-	8-(2)-thiophene
67	iso-pentyl	Ph-	9-methyl
68	iso-pentyl	Ph-	9-ethyl
69	iso-pentyl	Ph-	9-iso-propyl
70	iso-pentyl	Ph-	9-tert-butyl
71	iso-pentyl	Ph-	9-OH
72	iso-pentyl	Ph-	9-OCH_3
73	iso-pentyl	Ph-	9-O(iso-propyl)
74	iso-pentyl	Ph-	9-SCH_3
75	iso-pentyl	Ph-	9-$SOCH_3$
76	iso-pentyl	Ph-	9-SO_2CH_3
77	iso-pentyl	Ph-	9-SCH_2CH_3
78	iso-pentyl	Ph-	9-NH_2
79	iso-pentyl	Ph-	9-NHOH
80	iso-pentyl	Ph-	9-$NHCH_3$
81	iso-pentyl	Ph-	9-$N(CH_3)_2$
82	iso-pentyl	Ph-	9-$N^+(CH_3)_3$, I^-
83	iso-pentyl	Ph-	9-$NHC(=O)CH_3$
84	iso-pentyl	Ph-	9-$N(CH_2CH_3)_2$
85	iso-pentyl	Ph-	9-$NMeCH_2CO_2H$
86	iso-pentyl	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	iso-pentyl	Ph-	9-(N)-morpholine
88	iso-pentyl	Ph-	9-(N)-azetidino
89	iso-pentyl	Ph-	9-(N)-N-methylazetidinium, I^-
90	iso-pentyl	Ph-	9-(N)-pyrrolidino
91	iso-pentyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	iso-pentyl	Ph-	9-(N)-N-methyl-morpholinium, I^-

93	iso-pentyl	Ph-	9-(N)-N'-methylpiperazine
93	iso-pentyl	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	iso-pentyl	Ph-	9-NH-CBZ
96	iso-pentyl	Ph-	9-NHC(O)C_5H_{11}
97	iso-pentyl	Ph-	9-NHC(O)CH_2Br
98	iso-pentyl	Ph-	9-NH-C(NH)NH_2
99	iso-pentyl	Ph-	9-(2)-thiophene
100	iso-pentyl	Ph-	7-OCH_3, 8-OCH_3
101	iso-pentyl	Ph-	7-SCH_3, 8-OCH_3
102	iso-pentyl	Ph-	7-SCH_3, 8-SCH_3
103	iso-pentyl	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FTP,xxx,	Cpd# yyy)	R^1=R^2	R^5	$(R^x)q$
F101.008	01	$CH_2C(=O)C_2H_5$	Ph-	7-methyl
	02	$CH_2C(=O)C_2H_5$	Ph-	7-ethyl
	03	$CH_2C(=O)C_2H_5$	Ph-	7-iso-propyl
	04	$CH_2C(=O)C_2H_5$	Ph-	7-tert-butyl
	05	$CH_2C(=O)C_2H_5$	Ph-	7-OH
	06	$CH_2C(=O)C_2H_5$	Ph-	7-OCH_3
	07	$CH_2C(=O)C_2H_5$	Ph-	7-O(iso-propyl)
	08	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_3
	09	$CH_2C(=O)C_2H_5$	Ph-	7-$SOCH_3$
	10	$CH_2C(=O)C_2H_5$	Ph-	7-SO_2CH_3
	11	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_2CH_3
	12	$CH_2C(=O)C_2H_5$	Ph-	7-NH_2
	13	$CH_2C(=O)C_2H_5$	Ph-	7-NHOH
	14	$CH_2C(=O)C_2H_5$	Ph-	7-$NHCH_3$
	15	$CH_2C(=O)C_2H_5$	Ph-	7-$N(CH_3)_2$
	16	$CH_2C(=O)C_2H_5$	Ph-	7-$N^+(CH_3)_3$, I^-
	17	$CH_2C(=O)C_2H_5$	Ph-	7-$NHC(=O)CH_3$
	18	$CH_2C(=O)C_2H_5$	Ph-	7-$N(CH_2CH_3)_2$
	19	$CH_2C(=O)C_2H_5$	Ph-	7-$NMeCH_2CO_2H$
	20	$CH_2C(=O)C_2H_5$	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-morpholine
	22	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-azetidine
	23	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N-methylazetidinium, I^-
	24	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-pyrrolidine
	25	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N'-methylpiperazine
	28	$CH_2C(=O)C_2H_5$	Ph-	7-(N)-N'-dimethylpiperazinium, I^-

29	$CH_2C(=O)C_2H_5$	Ph-	7-NH-CBZ
30	$CH_2C(=O)C_2H_5$	Ph-	7-NHC(O)C_5H_{11}
31	$CH_2C(=O)C_2H_5$	Ph-	7-NHC(O)CH_2Br
32	$CH_2C(=O)C_2H_5$	Ph-	7-NH-C(NH)NH_2
33	$CH_2C(=O)C_2H_5$	Ph-	7-(2)-thiophene
34	$CH_2C(=O)C_2H_5$	Ph-	8-methyl
35	$CH_2C(=O)C_2H_5$	Ph-	8-ethyl
36	$CH_2C(=O)C_2H_5$	Ph-	8-iso-propyl
37	$CH_2C(=O)C_2H_5$	Ph-	8-tert-butyl
38	$CH_2C(=O)C_2H_5$	Ph-	8-OH
39	$CH_2C(=O)C_2H_5$	Ph-	8-OCH_3
40	$CH_2C(=O)C_2H_5$	Ph-	8-O(iso-propyl)
41	$CH_2C(=O)C_2H_5$	Ph-	8-SCH_3
42	$CH_2C(=O)C_2H_5$	Ph-	8-$SOCH_3$
43	$CH_2C(=O)C_2H_5$	Ph-	8-SO_2CH_3
44	$CH_2C(=O)C_2H_5$	Ph-	8-SCH_2CH_3
45	$CH_2C(=O)C_2H_5$	Ph-	8-NH_2
46	$CH_2C(=O)C_2H_5$	Ph-	8-NHOH
47	$CH_2C(=O)C_2H_5$	Ph-	8-$NHCH_3$
48	$CH_2C(=O)C_2H_5$	Ph-	8-$N(CH_3)_2$
49	$CH_2C(=O)C_2H_5$	Ph-	8-$N^+(CH_3)_3$, I^-
50	$CH_2C(=O)C_2H_5$	Ph-	8-$NHC(=O)CH_3$
51	$CH_2C(=O)C_2H_5$	Ph-	8-$N(CH_2CH_3)_2$
52	$CH_2C(=O)C_2H_5$	Ph-	8-$NMeCH_2CO_2H$
53	$CH_2C(=O)C_2H_5$	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-morpholine
55	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-azetidine
56	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N-methylazetidinium, I^-
57	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-pyrrolidine
58	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N'-methylpiperazine
61	$CH_2C(=O)C_2H_5$	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	$CH_2C(=O)C_2H_5$	Ph-	8-NH-CBZ
63	$CH_2C(=O)C_2H_5$	Ph-	8-NHC(O)C_5H_{11}
64	$CH_2C(=O)C_2H_5$	Ph-	8-NHC(O)CH_2Br
65	$CH_2C(=O)C_2H_5$	Ph-	8-NH-C(NH)NH_2
66	$CH_2C(=O)C_2H_5$	Ph-	8-(2)-thiophene
67	$CH_2C(=O)C_2H_5$	Ph-	9-methyl
68	$CH_2C(=O)C_2H_5$	Ph-	9-ethyl
69	$CH_2C(=O)C_2H_5$	Ph-	9-iso-propyl

70	$CH_2C(=O)C_2H_5$	Ph-	9-tert-butyl
71	$CH_2C(=O)C_2H_5$	Ph-	9-OH
72	$CH_2C(=O)C_2H_5$	Ph-	9-OCH_3
73	$CH_2C(=O)C_2H_5$	Ph-	9-O(iso-propyl)
74	$CH_2C(=O)C_2H_5$	Ph-	9-SCH_3
75	$CH_2C(=O)C_2H_5$	Ph-	9-$SOCH_3$
76	$CH_2C(=O)C_2H_5$	Ph-	9-SO_2CH_3
77	$CH_2C(=O)C_2H_5$	Ph-	9-SCH_2CH_3
78	$CH_2C(=O)C_2H_5$	Ph-	9-NH_2
79	$CH_2C(=O)C_2H_5$	Ph-	9-NHOH
80	$CH_2C(=O)C_2H_5$	Ph-	9-$NHCH_3$
81	$CH_2C(=O)C_2H_5$	Ph-	9-$N(CH_3)_2$
82	$CH_2C(=O)C_2H_5$	Ph-	9-$N^+(CH_3)_3$, I^-
83	$CH_2C(=O)C_2H_5$	Ph-	9-$NHC(=O)CH_3$
84	$CH_2C(=O)C_2H_5$	Ph-	9-$N(CH_2CH_3)_2$
85	$CH_2C(=O)C_2H_5$	Ph-	9-$NMeCH_2CO_2H$
86	$CH_2C(=O)C_2H_5$	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-morpholine
88	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-azetidine
89	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N-methylazetidinium, I^-
90	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-pyrrolidine
91	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N'-methylpiperazine
93	$CH_2C(=O)C_2H_5$	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	$CH_2C(=O)C_2H_5$	Ph-	9-NH-CBZ
96	$CH_2C(=O)C_2H_5$	Ph-	9-$NHC(O)C_5H_{11}$
97	$CH_2C(=O)C_2H_5$	Ph-	9-$NHC(O)CH_2Br$
98	$CH_2C(=O)C_2H_5$	Ph-	9-$NH-C(NH)NH_2$
99	$CH_2C(=O)C_2H_5$	Ph-	9-(2)-thiophene
100	$CH_2C(=O)C_2H_5$	Ph-	7-OCH_3, 8-OCH_3
101	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_3, 8-OCH_3
102	$CH_2C(=O)C_2H_5$	Ph-	7-SCH_3, 8-SCH_3
103	$CH_2C(=O)C_2H_5$	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.009	01	$CH_2OC_2H_5$	Ph-	7-methyl
	02	$CH_2OC_2H_5$	Ph-	7-ethyl
	03	$CH_2OC_2H_5$	Ph-	7-iso-propyl
	04	$CH_2OC_2H_5$	Ph-	7-tert-butyl

05	$CH_2OC_2H_5$	Ph-	7-OH
06	$CH_2OC_2H_5$	Ph-	7-OCH_3
07	$CH_2OC_2H_5$	Ph-	7-O(iso-propyl)
08	$CH_2OC_2H_5$	Ph-	7-SCH_3
09	$CH_2OC_2H_5$	Ph-	7-$SOCH_3$
10	$CH_2OC_2H_5$	Ph-	7-SO_2CH_3
11	$CH_2OC_2H_5$	Ph-	7-SCH_2CH_3
12	$CH_2OC_2H_5$	Ph-	7-NH_2
13	$CH_2OC_2H_5$	Ph-	7-NHOH
14	$CH_2OC_2H_5$	Ph-	7-$NHCH_3$
15	$CH_2OC_2H_5$	Ph-	7-$N(CH_3)_2$
16	$CH_2OC_2H_5$	Ph-	7-$N^+(CH_3)_3$, I^-
17	$CH_2OC_2H_5$	Ph-	7-$NHC(=O)CH_3$
18	$CH_2OC_2H_5$	Ph-	7-$N(CH_2CH_3)_2$
19	$CH_2OC_2H_5$	Ph-	7-$NMeCH_2CO_2H$
20	$CH_2OC_2H_5$	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
21	$CH_2OC_2H_5$	Ph-	7-(N)-morpholine
22	$CH_2OC_2H_5$	Ph-	7-(N)-azetidine
23	$CH_2OC_2H_5$	Ph-	7-(N)-N-methylazetidinium, I^-
24	$CH_2OC_2H_5$	Ph-	7-(N)-pyrrolidine
25	$CH_2OC_2H_5$	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	$CH_2OC_2H_5$	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	$CH_2OC_2H_5$	Ph-	7-(N)-N'-methylpiperazine
28	$CH_2OC_2H_5$	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	$CH_2OC_2H_5$	Ph-	7-NH-CBZ
30	$CH_2OC_2H_5$	Ph-	7-$NHC(O)C_5H_{11}$
31	$CH_2OC_2H_5$	Ph-	7-$NHC(O)CH_2Br$
32	$CH_2OC_2H_5$	Ph-	7-$NH-C(NH)NH_2$
33	$CH_2OC_2H_5$	Ph-	7-(2)-thiophene
34	$CH_2OC_2H_5$	Ph-	8-methyl
35	$CH_2OC_2H_5$	Ph-	8-ethyl
36	$CH_2OC_2H_5$	Ph-	8-iso-propyl
37	$CH_2OC_2H_5$	Ph-	8-tert-butyl
38	$CH_2OC_2H_5$	Ph-	8-OH
39	$CH_2OC_2H_5$	Ph-	8-OCH_3
40	$CH_2OC_2H_5$	Ph-	8-O(iso-propyl)
41	$CH_2OC_2H_5$	Ph-	8-SCH_3
42	$CH_2OC_2H_5$	Ph-	8-$SOCH_3$
43	$CH_2OC_2H_5$	Ph-	8-SO_2CH_3
44	$CH_2OC_2H_5$	Ph-	8-SCH_2CH_3
45	$CH_2OC_2H_5$	Ph-	8-NH_2
46	$CH_2OC_2H_5$	Ph-	8-NHOH

47	$CH_2OC_2H_5$	Ph-	8-$NHCH_3$
48	$CH_2OC_2H_5$	Ph-	8-$N(CH_3)_2$
49	$CH_2OC_2H_5$	Ph-	8-$N^+(CH_3)_3$, I^-
50	$CH_2OC_2H_5$	Ph-	8-$NHC(=O)CH_3$
51	$CH_2OC_2H_5$	Ph-	8-$N(CH_2CH_3)_2$
52	$CH_2OC_2H_5$	Ph-	8-$NMeCH_2CO_2H$
53	$CH_2OC_2H_5$	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	$CH_2OC_2H_5$	Ph-	8-(N)-morpholine
55	$CH_2OC_2H_5$	Ph-	8-(N)-azetidine
56	$CH_2OC_2H_5$	Ph-	8-(N)-N-methylazetidinium, I^-
57	$CH_2OC_2H_5$	Ph-	8-(N)-pyrrolidine
58	$CH_2OC_2H_5$	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	$CH_2OC_2H_5$	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	$CH_2OC_2H_5$	Ph-	8-(N)-N'-methylpiperazine
61	$CH_2OC_2H_5$	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	$CH_2OC_2H_5$	Ph-	8-NH-CBZ
63	$CH_2OC_2H_5$	Ph-	8-$NHC(O)C_5H_{11}$
64	$CH_2OC_2H_5$	Ph-	8-$NHC(O)CH_2Br$
65	$CH_2OC_2H_5$	Ph-	8-$NH-C(NH)NH_2$
66	$CH_2OC_2H_5$	Ph-	8-(2)-thiophene
67	$CH_2OC_2H_5$	Ph-	9-methyl
68	$CH_2OC_2H_5$	Ph-	9-ethyl
69	$CH_2OC_2H_5$	Ph-	9-iso-propyl
70	$CH_2OC_2H_5$	Ph-	9-tert-butyl
71	$CH_2OC_2H_5$	Ph-	9-OH
72	$CH_2OC_2H_5$	Ph-	9-OCH_3
73	$CH_2OC_2H_5$	Ph-	9-O(iso-propyl)
74	$CH_2OC_2H_5$	Ph-	9-SCH_3
75	$CH_2OC_2H_5$	Ph-	9-$SOCH_3$
76	$CH_2OC_2H_5$	Ph-	9-SO_2CH_3
77	$CH_2OC_2H_5$	Ph-	9-SCH_2CH_3
78	$CH_2OC_2H_5$	Ph-	9-NH_2
79	$CH_2OC_2H_5$	Ph-	9-NHOH
80	$CH_2OC_2H_5$	Ph-	9-$NHCH_3$
81	$CH_2OC_2H_5$	Ph-	9-$N(CH_3)_2$
82	$CH_2OC_2H_5$	Ph-	9-$N^+(CH_3)_3$, I^-
83	$CH_2OC_2H_5$	Ph-	9-$NHC(=O)CH_3$
84	$CH_2OC_2H_5$	Ph-	9-$N(CH_2CH_3)_2$
85	$CH_2OC_2H_5$	Ph-	9-$NMeCH_2CO_2H$
86	$CH_2OC_2H_5$	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	$CH_2OC_2H_5$	Ph-	9-(N)-morpholine

88	$CH_2OC_2H_5$	Ph-	9-(N)-azetidine
89	$CH_2OC_2H_5$	Ph-	9-(N)-N-methylazetidinium, I^-
90	$CH_2OC_2H_5$	Ph-	9-(N)-pyrrolidine
91	$CH_2OC_2H_5$	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	$CH_2OC_2H_5$	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	$CH_2OC_2H_5$	Ph-	9-(N)-N'-methylpiperazine
93	$CH_2OC_2H_5$	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	$CH_2OC_2H_5$	Ph-	9-NH-CBZ
96	$CH_2OC_2H_5$	Ph-	9-$NHC(O)C_5H_{11}$
97	$CH_2OC_2H_5$	Ph-	9-$NHC(O)CH_2Br$
98	$CH_2OC_2H_5$	Ph-	9-$NH-C(NH)NH_2$
99	$CH_2OC_2H_5$	Ph-	9-(2)-thiophene
100	$CH_2OC_2H_5$	Ph-	7-OCH_3, 8-OCH_3
101	$CH_2OC_2H_5$	Ph-	7-SCH_3, 8-OCH_3
102	$CH_2OC_2H_5$	Ph-	7-SCH_3, 8-SCH_3
103	$CH_2OC_2H_5$	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.010	01	$CH_2CH(OH)C_2H_5$	Ph-	7-methyl
	02	$CH_2CH(OH)C_2H_5$	Ph-	7-ethyl
	03	$CH_2CH(OH)C_2H_5$	Ph-	7-iso-propyl
	04	$CH_2CH(OH)C_2H_5$	Ph-	7-tert-butyl
	05	$CH_2CH(OH)C_2H_5$	Ph-	7-OH
	06	$CH_2CH(OH)C_2H_5$	Ph-	7-OCH_3
	07	$CH_2CH(OH)C_2H_5$	Ph-	7-O(iso-propyl)
	08	$CH_2CH(OH)C_2H_5$	Ph-	7-SCH_3
	09	$CH_2CH(OH)C_2H_5$	Ph-	7-$SOCH_3$
	10	$CH_2CH(OH)C_2H_5$	Ph-	7-SO_2CH_3
	11	$CH_2CH(OH)C_2H_5$	Ph-	7-SCH_2CH_3
	12	$CH_2CH(OH)C_2H_5$	Ph-	7-NH_2
	13	$CH_2CH(OH)C_2H_5$	Ph-	7-NHOH
	14	$CH_2CH(OH)C_2H_5$	Ph-	7-$NHCH_3$
	15	$CH_2CH(OH)C_2H_5$	Ph-	7-$N(CH_3)_2$
	16	$CH_2CH(OH)C_2H_5$	Ph-	7-$N^+(CH_3)_3$, I^-
	17	$CH_2CH(OH)C_2H_5$	Ph-	7-$NHC(=O)CH_3$
	18	$CH_2CH(OH)C_2H_5$	Ph-	7-$N(CH_2CH_3)_2$
	19	$CH_2CH(OH)C_2H_5$	Ph-	7-$NMeCH_2CO_2H$
	20	$CH_2CH(OH)C_2H_5$	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-morpholine
	22	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-azetidine

23	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N-methylazetidinium, I^-
24	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-pyrrolidine
25	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
26	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N-methyl-morpholinium, I^-
27	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N'-methylpiperazine
28	$CH_2CH(OH)C_2H_5$	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
29	$CH_2CH(OH)C_2H_5$	Ph-	7-NH-CBZ
30	$CH_2CH(OH)C_2H_5$	Ph-	$7\text{-}NHC(O)C_5H_{11}$
31	$CH_2CH(OH)C_2H_5$	Ph-	$7\text{-}NHC(O)CH_2Br$
32	$CH_2CH(OH)C_2H_5$	Ph-	$7\text{-}NH\text{-}C(NH)NH_2$
33	$CH_2CH(OH)C_2H_5$	Ph-	7-(2)-thiophene
34	$CH_2CH(OH)C_2H_5$	Ph-	8-methyl
35	$CH_2CH(OH)C_2H_5$	Ph-	8-ethyl
36	$CH_2CH(OH)C_2H_5$	Ph-	8-iso-propyl
37	$CH_2CH(OH)C_2H_5$	Ph-	8-tert-butyl
38	$CH_2CH(OH)C_2H_5$	Ph-	8-OH
39	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}OCH_3$
40	$CH_2CH(OH)C_2H_5$	Ph-	8-O(iso-propyl)
41	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}SCH_3$
42	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}SOCH_3$
43	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}SO_2CH_3$
44	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}SCH_2CH_3$
45	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NH_2$
46	$CH_2CH(OH)C_2H_5$	Ph-	8-NHOH
47	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NHCH_3$
48	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}N(CH_3)_2$
49	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}N^+(CH_3)_3$, I^-
50	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NHC(=O)CH_3$
51	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}N(CH_2CH_3)_2$
52	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NMeCH_2CO_2H$
53	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}N^+(Me)_2CH_2CO_2H$, I^-
54	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-morpholine
55	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-azetidine
56	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N-methylazetidinium, I^-
57	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-pyrrolidine
58	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N'-methylpiperazine
61	$CH_2CH(OH)C_2H_5$	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	$CH_2CH(OH)C_2H_5$	Ph-	8-NH-CBZ
63	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NHC(O)C_5H_{11}$
64	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NHC(O)CH_2Br$

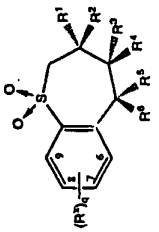
65	$CH_2CH(OH)C_2H_5$	Ph-	$8\text{-}NH\text{-}C(NH)NH_2$
66	$CH_2CH(OH)C_2H_5$	Ph-	8-(2)-thiophene
67	$CH_2CH(OH)C_2H_5$	Ph-	9-methyl
68	$CH_2CH(OH)C_2H_5$	Ph-	9-ethyl
69	$CH_2CH(OH)C_2H_5$	Ph-	9-iso-propyl
70	$CH_2CH(OH)C_2H_5$	Ph-	9-tert-butyl
71	$CH_2CH(OH)C_2H_5$	Ph-	9-OH
72	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}OCH_3$
73	$CH_2CH(OH)C_2H_5$	Ph-	9-O(iso-propyl)
74	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}SCH_3$
75	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}SOCH_3$
76	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}SO_2CH_3$
77	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}SCH_2CH_3$
78	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NH_2$
79	$CH_2CH(OH)C_2H_5$	Ph-	9-NHOH
80	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NHCH_3$
81	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}N(CH_3)_2$
82	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}N^+(CH_3)_3$, I^-
83	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NHC(=O)CH_3$
84	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}N(CH_2CH_3)_2$
85	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NMeCH_2CO_2H$
86	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}N^+(Me)_2CH_2CO_2H$, I^-
87	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-morpholine
88	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-azetidine
89	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N-methylazetidinium, I^-
90	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-pyrrolidine
91	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N'-methylpiperazine
93	$CH_2CH(OH)C_2H_5$	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	$CH_2CH(OH)C_2H_5$	Ph-	9-NH-CBZ
96	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NHC(O)C_5H_{11}$
97	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NHC(O)CH_2Br$
98	$CH_2CH(OH)C_2H_5$	Ph-	$9\text{-}NH\text{-}C(NH)NH_2$
99	$CH_2CH(OH)C_2H_5$	Ph-	9-(2)-thiophene
100	$CH_2CH(OH)C_2H_5$	Ph-	$7\text{-}OCH_3$, $8\text{-}OCH_3$
101	$CH_2CH(OH)C_2H_5$	Ph-	$7\text{-}SCH_3$, $8\text{-}OCH_3$
102	$CH_2CH(OH)C_2H_5$	Ph-	$7\text{-}SCH_3$, $8\text{-}SCH_3$
103	$CH_2CH(OH)C_2H_5$	Ph-	$6\text{-}OCH_3$, $7\text{-}OCH_3$, $8\text{-}OCH_3$

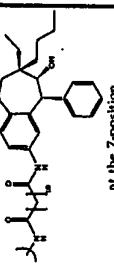
Prefix (FFF.xxx.	Cpd# yyy)	R^1=R^2	R^5	$(R^x)_q$
F101.011	01	CH_2O-(4-picoline)	Ph-	7-methyl
	02	CH_2O-(4-picoline)	Ph-	7-ethyl
	03	CH_2O-(4-picoline)	Ph-	7-iso-propyl
	04	CH_2O-(4-picoline)	Ph-	7-tert-butyl
	05	CH_2O-(4-picoline)	Ph-	7-OH
	06	CH_2O-(4-picoline)	Ph-	7-OCH_3
	07	CH_2O-(4-picoline)	Ph-	7-O(iso-propyl)
	08	CH_2O-(4-picoline)	Ph-	7-SCH_3
	09	CH_2O-(4-picoline)	Ph-	7-$SOCH_3$
	10	CH_2O-(4-picoline)	Ph-	7-SO_2CH_3
	11	CH_2O-(4-picoline)	Ph-	7-SCH_2CH_3
	12	CH_2O-(4-picoline)	Ph-	7-NH_2
	13	CH_2O-(4-picoline)	Ph-	7-NHOH
	14	CH_2O-(4-picoline)	Ph-	7-$NHCH_3$
	15	CH_2O-(4-picoline)	Ph-	7-$N(CH_3)_2$
	16	CH_2O-(4-picoline)	Ph-	7-$N^+(CH_3)_3$, I^-
	17	CH_2O-(4-picoline)	Ph-	7-$NHC(=O)CH_3$
	18	CH_2O-(4-picoline)	Ph-	7-$N(CH_2CH_3)_2$
	19	CH_2O-(4-picoline)	Ph-	7-$NMeCH_2CO_2H$
	20	CH_2O-(4-picoline)	Ph-	7-$N^+(Me)_2CH_2CO_2H$, I^-
	21	CH_2O-(4-picoline)	Ph-	7-(N)-morpholine
	22	CH_2O-(4-picoline)	Ph-	7-(N)-azetidine
	23	CH_2O-(4-picoline)	Ph-	7-(N)-N-methylazetidinium, I^-
	24	CH_2O-(4-picoline)	Ph-	7-(N)-pyrrolidine
	25	CH_2O-(4-picoline)	Ph-	7-(N)-N-methyl-pyrrolidinium, I^-
	26	CH_2O-(4-picoline)	Ph-	7-(N)-N-methyl-morpholinium, I^-
	27	CH_2O-(4-picoline)	Ph-	7-(N)-N'-methylpiperazine
	28	CH_2O-(4-picoline)	Ph-	7-(N)-N'-dimethylpiperazinium, I^-
	29	CH_2O-(4-picoline)	Ph-	7-NH-CBZ
	30	CH_2O-(4-picoline)	Ph-	7-$NHC(O)C_5H_{11}$
	31	CH_2O-(4-picoline)	Ph-	7-$NHC(O)CH_2Br$
	32	CH_2O-(4-picoline)	Ph-	7-$NH-C(NH)NH_2$
	33	CH_2O-(4-picoline)	Ph-	7-(2)-thiophene
	34	CH_2O-(4-picoline)	Ph-	8-methyl
	35	CH_2O-(4-picoline)	Ph-	8-ethyl
	36	CH_2O-(4-picoline)	Ph-	8-iso-propyl
	37	CH_2O-(4-picoline)	Ph-	8-tert-butyl
	38	CH_2O-(4-picoline)	Ph-	8-OH
	39	CH_2O-(4-picoline)	Ph-	8-OCH_3

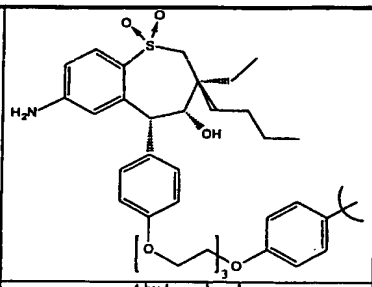
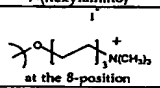
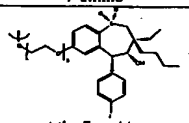
40	CH_2O-(4-picoline)	Ph-	8-O(iso-propyl)
41	CH_2O-(4-picoline)	Ph-	8-SCH_3
42	CH_2O-(4-picoline)	Ph-	8-$SOCH_3$
43	CH_2O-(4-picoline)	Ph-	8-SO_2CH_3
44	CH_2O-(4-picoline)	Ph-	8-SCH_2CH_3
45	CH_2O-(4-picoline)	Ph-	8-NH_2
46	CH_2O-(4-picoline)	Ph-	8-NHOH
47	CH_2O-(4-picoline)	Ph-	8-$NHCH_3$
48	CH_2O-(4-picoline)	Ph-	8-$N(CH_3)_2$
49	CH_2O-(4-picoline)	Ph-	8-$N^+(CH_3)_3$, I^-
50	CH_2O-(4-picoline)	Ph-	8-$NHC(=O)CH_3$
51	CH_2O-(4-picoline)	Ph-	8-$N(CH_2CH_3)_2$
52	CH_2O-(4-picoline)	Ph-	8-$NMeCH_2CO_2H$
53	CH_2O-(4-picoline)	Ph-	8-$N^+(Me)_2CH_2CO_2H$, I^-
54	CH_2O-(4-picoline)	Ph-	8-(N)-morpholine
55	CH_2O-(4-picoline)	Ph-	8-(N)-azetidine
56	CH_2O-(4-picoline)	Ph-	8-(N)-N-methylazetidinium, I^-
57	CH_2O-(4-picoline)	Ph-	8-(N)-pyrrolidine
58	CH_2O-(4-picoline)	Ph-	8-(N)-N-methyl-pyrrolidinium, I^-
59	CH_2O-(4-picoline)	Ph-	8-(N)-N-methyl-morpholinium, I^-
60	CH_2O-(4-picoline)	Ph-	8-(N)-N'-methylpiperazine
61	CH_2O-(4-picoline)	Ph-	8-(N)-N'-dimethylpiperazinium, I^-
62	CH_2O-(4-picoline)	Ph-	8-NH-CBZ
63	CH_2O-(4-picoline)	Ph-	8-$NHC(O)C_5H_{11}$
64	CH_2O-(4-picoline)	Ph-	8-$NHC(O)CH_2Br$
65	CH_2O-(4-picoline)	Ph-	8-$NH-C(NH)NH_2$
66	CH_2O-(4-picoline)	Ph-	8-(2)-thiophene
67	CH_2O-(4-picoline)	Ph-	9-methyl
68	CH_2O-(4-picoline)	Ph-	9-ethyl
69	CH_2O-(4-picoline)	Ph-	9-iso-propyl
70	CH_2O-(4-picoline)	Ph-	9-tert-butyl
71	CH_2O-(4-picoline)	Ph-	9-OH
72	CH_2O-(4-picoline)	Ph-	9-OCH_3
73	CH_2O-(4-picoline)	Ph-	9-O(iso-propyl)
74	CH_2O-(4-picoline)	Ph-	9-SCH_3
75	CH_2O-(4-picoline)	Ph-	9-$SOCH_3$
76	CH_2O-(4-picoline)	Ph-	9-SO_2CH_3
77	CH_2O-(4-picoline)	Ph-	9-SCH_2CH_3
78	CH_2O-(4-picoline)	Ph-	9-NH_2
79	CH_2O-(4-picoline)	Ph-	9-NHOH
80	CH_2O-(4-picoline)	Ph-	9-$NHCH_3$
81	CH_2O-(4-picoline)	Ph-	9-$N(CH_3)_2$

82	CH_2O-(4-picoline)	Ph-	9-$N^+(CH_3)_3$, I^-
83	CH_2O-(4-picoline)	Ph-	9-NHC(=O)CH_3
84	CH_2O-(4-picoline)	Ph-	9-$N(CH_2CH_3)_2$
85	CH_2O-(4-picoline)	Ph-	9-$NMeCH_2CO_2H$
86	CH_2O-(4-picoline)	Ph-	9-$N^+(Me)_2CH_2CO_2H$, I^-
87	CH_2O-(4-picoline)	Ph-	9-(N)-morpholine
88	CH_2O-(4-picoline)	Ph-	9-(N)-azetidine
89	CH_2O-(4-picoline)	Ph-	9-(N)-N-methylazetidinium, I^-
90	CH_2O-(4-picoline)	Ph-	9-(N)-pyrrolidine
91	CH_2O-(4-picoline)	Ph-	9-(N)-N-methyl-pyrrolidinium, I^-
92	CH_2O-(4-picoline)	Ph-	9-(N)-N-methyl-morpholinium, I^-
93	CH_2O-(4-picoline)	Ph-	9-(N)-N'-methylpiperazine
93	CH_2O-(4-picoline)	Ph-	9-(N)-N'-dimethylpiperazinium, I^-
95	CH_2O-(4-picoline)	Ph-	9-NH-CBZ
96	CH_2O-(4-picoline)	Ph-	9-NHC(O)C_5H_{11}
97	CH_2O-(4-picoline)	Ph-	9-NHC(O)CH_2Br
98	CH_2O-(4-picoline)	Ph-	9-NH-C(NH)NH_2
99	CH_2O-(4-picoline)	Ph-	9-(2)-thiophene
100	CH_2O-(4-picoline)	Ph-	7-OCH_3, 8-OCH_3
101	CH_2O-(4-picoline)	Ph-	7-SCH_3, 8-OCH_3
102	CH_2O-(4-picoline)	Ph-	7-SCH_3, 8-SCH3
103	CH_2O-(4-picoline)	Ph-	6-OCH_3, 7-OCH_3, 8-OCH_3

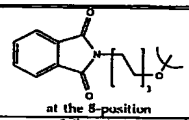
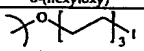
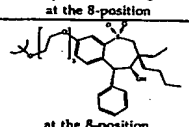
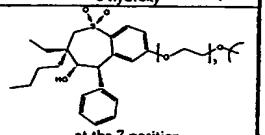
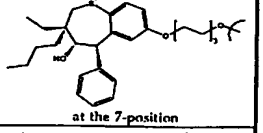
Additional Structures of the Present Invention



Compound Number	R^1	R^2	R^3	R^4	R^5	$(R^7)_q$
101	ethyl	n-butyl	OH	H	H	 at the 7-position
102	ethyl	n-butyl	OH	H	H	7-trimethylammonium iodide
103	n-butyl	ethyl	OH	H	H	7-trimethylammonium iodide
104	ethyl	n-butyl	OH	H	H	7-dimethylamino
105	ethyl	n-butyl	OH	H	H	7-methanesulfonamido
106	ethyl	n-butyl	OH	H	H	7-(2'-bromoacetamido)
107	n-butyl	ethyl	OH	H	H	7-amino
108	ethyl	n-butyl	OH	H	H	7-(hexylamido)
109	ethyl	n-butyl	OH	H	H	7-amino
110	ethyl	n-butyl	OH	H	H	7-acetamido
111	n-butyl	ethyl	OH	H	H	7-amino

112	ethyl	n-butyl	OH	H		H	7-amino
113	ethyl	n-butyl	OH	H	4-hydroxyphenyl	H	7-amino
114	ethyl	n-butyl	OH	H	4-methoxyphenyl	H	7-amino
115	n-butyl	ethyl	OH	H	4-methoxyphenyl	H	7-(O-benzylcarbamato)
116	ethyl	n-butyl	OH	H	4-methoxyphenyl	H	7-(O-benzylcarbamato)
117	n-butyl	ethyl	OH	H	phenyl	H	7-(O-benzylcarbamato)
118	ethyl	n-butyl	OH	H	phenyl	H	7-(O-benzylcarbamato)
119	ethyl	n-butyl	OH	H	phenyl	H	7-(O-tert-butylcarbamato)
120	n-butyl	ethyl	OH	H	phenyl	H	7-(O-benzylcarbamato)
121	ethyl	n-butyl	OH	H	phenyl	H	7-amino
122	n-butyl	ethyl	OH	H	phenyl	H	7-amino
123	ethyl	n-butyl	OH	H	phenyl	H	7-hexylamino
124	n-butyl	ethyl	OH	H	phenyl	H	7-(hexylamino)
125	ethyl	n-butyl	OH	H	phenyl	H	 at the 8-position
126	n-butyl	ethyl	OH	H	4-fluorophenyl	H	7-(O-benzylcarbamato)
127	n-butyl	ethyl	OH	H	4-fluorophenyl	H	7-amino
128	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-(O-benzylcarbamato)
129	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-amino
131	ethyl	n-butyl	OH	H	4-fluorophenyl	H	 at the 7-position

61

132	ethyl	n-butyl	OH	H	phenyl	H	 at the 8-position
133	ethyl	n-butyl	OH	H	phenyl	H	8-(hexyloxy)
134	ethyl	n-butyl	OH	H	phenyl	H	 at the 8-position
135	ethyl	n-butyl	OH	H	phenyl	H	 at the 8-position
136	ethyl	n-butyl	OH	H	phenyl	H	8-hydroxy
137	n-butyl	ethyl	OH	H	phenyl	H	 at the 7-position
138	n-butyl	ethyl	OH	H	phenyl	H	8-acetoxy
139	n-butyl	ethyl	OH	H	phenyl	H	 at the 7-position
140							
141							
142	ethyl	n-butyl	H	OH	H	3-methoxy-phenyl	7-methylmercapto
143	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-methylmercapto
144	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-(N-azetidinyl)
262	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-methoxy
263	ethyl	n-butyl	H	OH	H	3-methoxy-	7-methoxy

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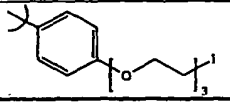
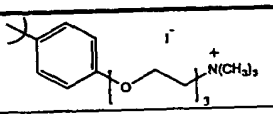
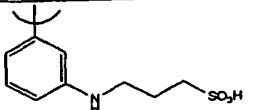
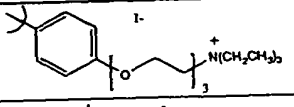
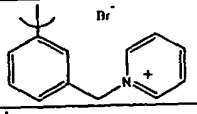
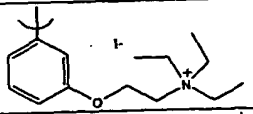
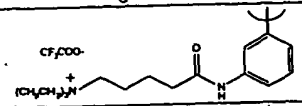
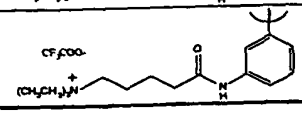
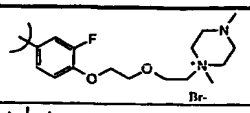
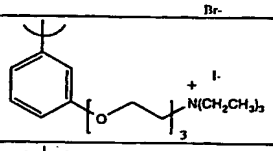
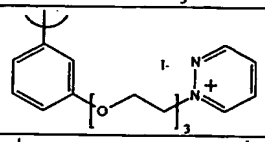
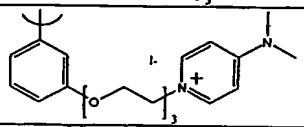
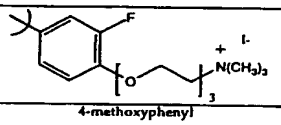
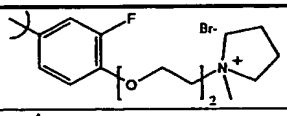
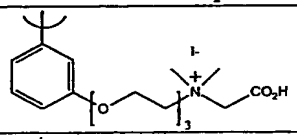
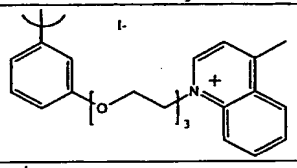
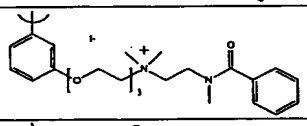
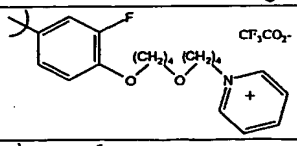
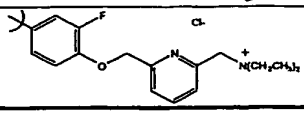
						phenyl	
264	ethyl	n-butyl	OH	H	3-trifluoromethylphenyl	H	7-methoxy
265	ethyl	n-butyl	H	OH	H	3-trifluoro-methyl-phenyl	7-methoxy
266	ethyl	n-butyl	OH	H	3-hydroxyphenyl	H	7-hydroxy
267	ethyl	n-butyl	OH	H	3-hydroxyphenyl	H	7-methoxy
268	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-methoxy
269	ethyl	n-butyl	H	OH	H	4-fluoro-phenyl	7-methoxy
270	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-hydroxy
271	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-bromo
272	ethyl	n-butyl	H	OH	H	3-methoxy-phenyl	7-bromo
273	ethyl	n-butyl	H	OH	H	4-fluoro-phenyl	7-fluoro
274	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-fluoro
275	ethyl	n-butyl	H	OH	H	3-methoxy-phenyl	7-fluoro
276	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-fluoro
277	ethyl	n-butyl	OH	H	3-fluorophenyl	H	7-methoxy
278	ethyl	n-butyl	H	OH	2-fluorophenyl	H	7-methoxy
279	ethyl	n-butyl	H	OH	3-fluorophenyl	H	7-methoxy
280	ethyl	n-butyl	OH	H	2-fluorophenyl	H	7-methoxy
281	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-methylmercapto
282	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-methyl
283	ethyl	n-butyl	H	OH	H	4-fluoro-phenyl	7-methyl
284	ethyl	n-butyl	OH	H	4-fluorophenyl	H	7-(4'-morpholino)
285					MISSING		
286	ethyl	ethyl	OH	H	phenyl	H	7-(O-benzylcarbamato)
287	ethyl	ethyl	OH	H	phenyl	H	7-amino
288	methyl	methyl	OH	H	phenyl	H	7-amino
289	n-butyl	n-butyl	OH	H	phenyl	H	7-amino
290	n-butyl	n-butyl	OH	H	phenyl	H	7-amino
291	n-butyl	n-butyl	OH	H	phenyl	H	7-(O-benzylcarbamato)
292	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-amino
293	n-butyl	n-butyl	OH	H	phenyl	H	7-benzylamino
294	n-butyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
295	ethyl	n-butyl	OH	H		H	7-amino

296	ethyl	n-butyl	OH	H		H	7-amino
1000	ethyl	n-butyl	OH	H		H	7-dimethylamino
1001	ethyl	n-butyl	OH	H		H	7-dimethylamino
1002	ethyl	n-butyl	OH	H		H	7-dimethylamino
1003	ethyl	n-butyl	OH	H		H	7-dimethylamino
1004	ethyl	n-butyl	OH	H		H	7-dimethylamino
1005	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1006	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1007	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1008	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1009	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1010	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-dimethylamino
1011	n-butyl	n-butyl	OH	H	3-fluoro-4-(5-triethylammoniumpentyloxy)phenyl, trifluoroacetate salt	H	7-dimethylamino
1012	n-butyl	n-butyl	OH	H	4-hydroxyphenyl	H	7-dimethylamino; 9-methoxy
1013	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1014	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	7-dimethylamino; 9-methoxy

1015	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1016	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1017	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1018	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1019	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1020	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1021	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1022	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1023	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1024	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1025	n-butyl	n-butyl	OH	H		H	7-dimethylamino
102A	n-butyl	n-butyl	OH	H		H	7-dimethylamino
102Z	n-butyl	n-butyl	OH	H		H	7-dimethylamino
102A	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1029	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1030	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1031	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1032	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1033	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1034	n-butyl	n-butyl	OH	H		H	7-dimethylamino

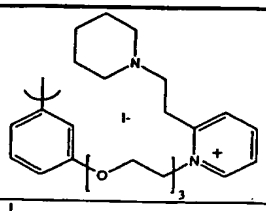
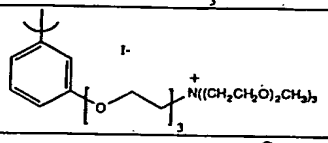
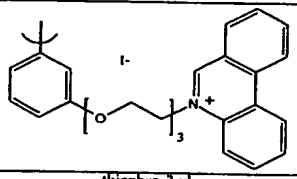
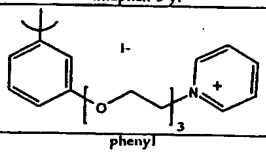
1035	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1036	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1037	n-butyl	n-butyl	OH	H	4-hydroxyphenyl	H	7-dimethylamino
1038	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1039	n-butyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
1040	n-butyl	n-butyl	OH	H	???How does this differ from 73281?	H	7-dimethylamino

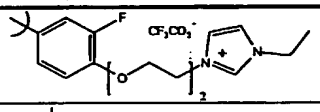
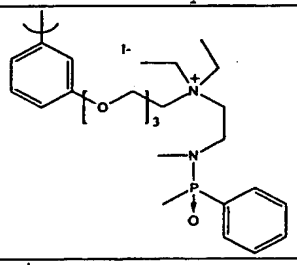
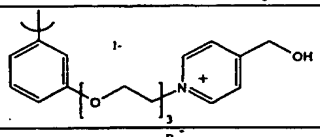
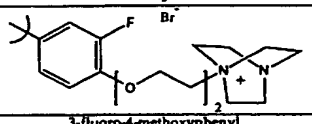
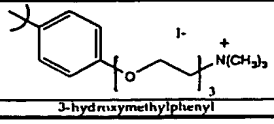
1041	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1042	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1043	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1044	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1045	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1046	n-butyl	n-butyl	OH	H	3-aminophenyl	H	7-dimethylamino
1047	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1048	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1049	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1050	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1051	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1052	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1053	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1054	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1055	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1056	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1057	n-butyl	n-butyl	OH	H		H	7-dimethylamino

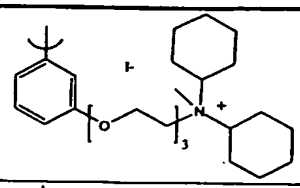
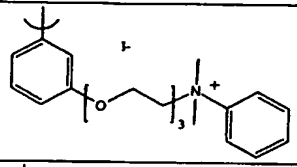
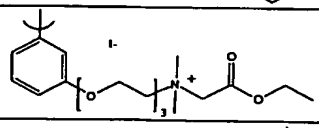
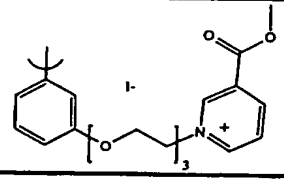
1058	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1059	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1060	ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-methylamino
1061	n-butyl	n-butyl	OH	H		H	7-methylamino
1062	n-butyl	n-butyl	OH	H		H	7-methylamino
1063	n-butyl	n-butyl	OH	H		H	7-methylamino

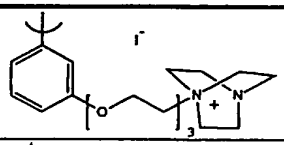
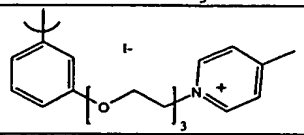
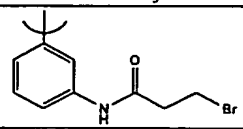
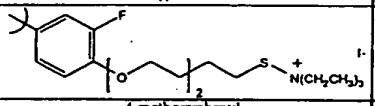
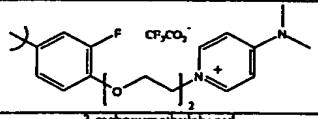
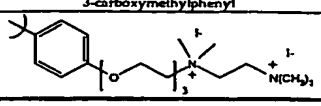
1064	n-butyl	n-butyl	OH	H		H	7-methylamino
1065	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1066	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1067	n-butyl	n-butyl	OH	H	thiophen-3-yl	H	9-dimethylamino
1068	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1069	n-butyl	n-butyl	OH	H	phenyl	H	7-dimethylamino; 9-dimethylamino

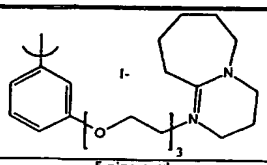
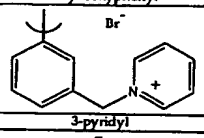
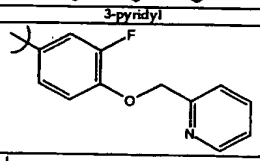
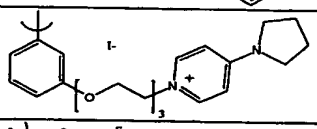
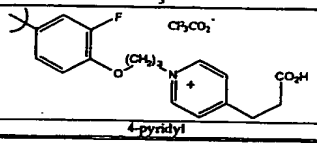
1070	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1071	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1072	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1073	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1074	ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-dimethylamino
1075	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-dimethylamino; 9-dimethylamino
1076	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1077	n-butyl	n-butyl	OH	H	3-hydroxymethylphenyl	H	7-dimethylamino

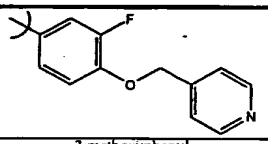
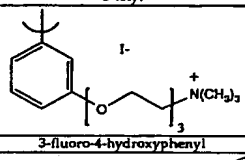
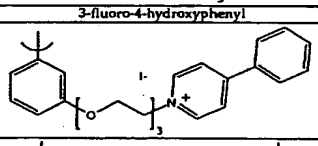
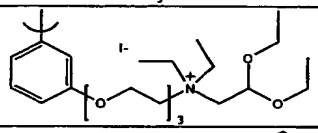
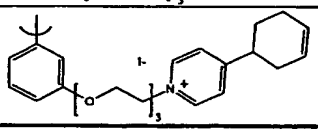
1078	ethyl	n-butyl	OH	H	4-hydroxyphenyl	H	7-dimethylamino
1079	ethyl	n-butyl	OH	H		H	7-dimethylamino
1080	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1081	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1082	n-butyl	n-butyl	OH	H	2-pyridyl	H	7-dimethylamino

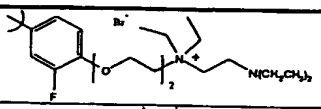
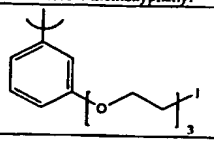
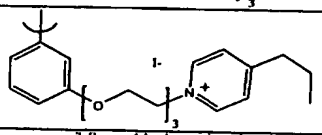
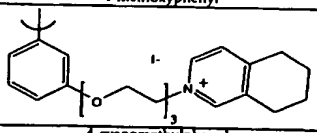
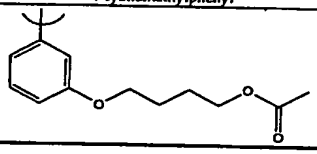
1083	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1084	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1085	n-butyl	n-butyl	OH	H	thiophen-3-yl	H	7-dimethylamino
1086	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1087	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1088	ethyl	n-butyl	OH	H	3,4-methylenedioxyphenyl	H	7-dimethylamino
1089	ethyl	n-butyl	OH	H	4-methoxyphenyl	H	7-dimethylamino
1090	n-butyl	n-butyl	OH	H		H	7-dimethylamino

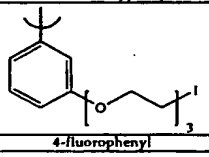
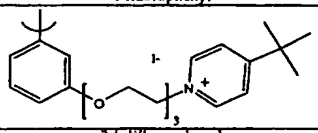
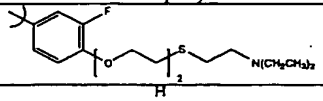
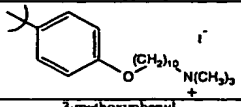
1091	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1092	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1093	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1094	n-butyl	n-butyl	OH	H		H	7-dimethylamino

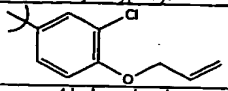
1095	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1096	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1097	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1098	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1099	ethyl	n-butyl	OH	H	4-methoxyphenyl	H	7-dimethylamino
1100	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	7-dimethylamino
1101	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1102	n-butyl	n-butyl	OH	H	3-carboxymethylphenyl	H	7-dimethylamino
1103	n-butyl	n-butyl	OH	H		H	7-dimethylamino

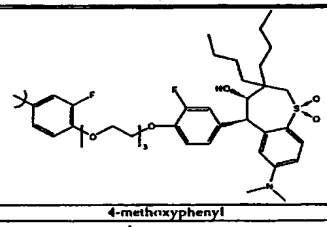
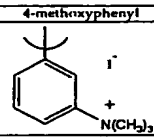
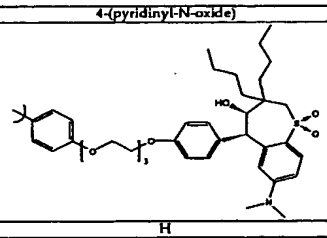
1104	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1105	n-butyl	n-butyl	OH	H	5-piperonyl	H	7-dimethylamino
1106	n-butyl	n-butyl	OH	H	3-hydroxyphenyl	H	7-dimethylamino
1107	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1108	n-butyl	n-butyl	OH	H	3-pyridyl	H	7-dimethylamino
1109	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1110	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1111	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1112	n-butyl	n-butyl	OH	H	4-pyridyl	H	7-dimethylamino

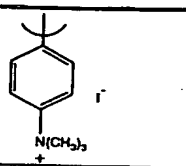
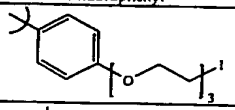
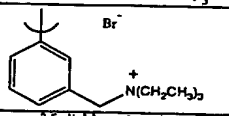
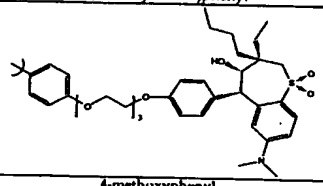
1113	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1114	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-methylamino
1115	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-dimethylamino
1116	ethyl	n-butyl	OH	H	3-tolyl	H	7-dimethylamino
1117	ethyl	n-butyl	OH	H		H	7-dimethylamino
1118	ethyl	n-butyl	OH	H	3-fluoro-4-hydroxyphenyl	H	7-dimethylamino
1119	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1120	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1121	n-butyl	n-butyl	OH	H		H	7-dimethylamino

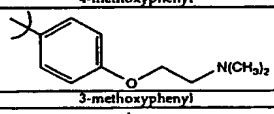
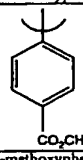
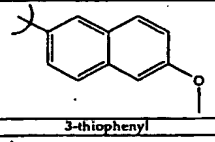
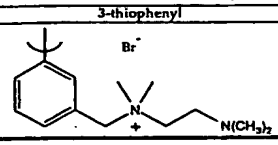
1122	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1123	n-butyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
1124	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-dimethylamino
1125	n-butyl	n-butyl	OH	H	3-chloro-4-methoxyphenyl	H	7-dimethylamino
1126	ethyl	n-butyl	OH	H		H	7-dimethylamino
1127	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1128	n-butyl	n-butyl	OH	H	3-fluoro-4-hydroxyphenyl	H	7-dimethylamino
1129	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-dimethylamino
1130	n-butyl	n-butyl	OH	H	3-chloro-4-fluorophenyl	H	7-dimethylamino
1131	ethyl	n-butyl	OH	H	4-methoxyphenyl	H	7-dimethylamino
1132	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1133	n-butyl	n-butyl	OH	H	4-cyanomethylphenyl	H	7-dimethylamino
1134	ethyl	n-butyl	OH	H		H	7-dimethylamino

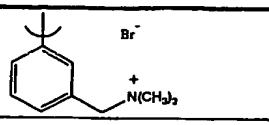
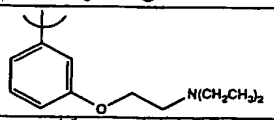
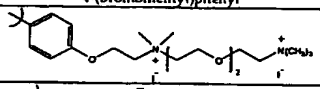
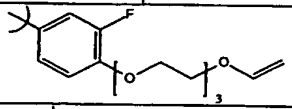
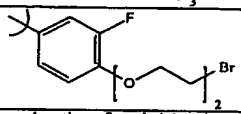
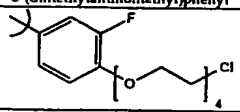
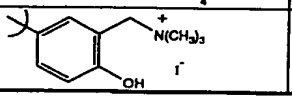
1135	n-butyl	n-butyl	OH	H	3,4-dimethoxyphenyl	H	7-dimethylamino
1136	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1137	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-(2',2'-dimethylhydrazino)
1138	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1139	n-butyl	n-butyl	OH	H	3,4-difluorophenyl	H	7-dimethylamino
1140	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-(2',2'-dimethylhydrazino)
1141	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-ethylmethylamino
1142	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1143	n-butyl	n-butyl	H	OH	H	3-fluoro-4-methoxy-phenyl	7-dimethylamino
1144	n-butyl	n-butyl	OH	H	5-piperonyl	H	7-dimethylamino
1145	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	9-dimethylamino
1146	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1147	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-diethylamino
1148	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-dimethylsulfonium, fluoride salt
1149	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-ethylamino
1150	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-ethylmethylamino
1151	n-butyl	ethyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-dimethylamino
1152	n-butyl	n-butyl	OH	H	phenyl	H	7-(ethoxymethyl) methylamino
1153	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-methylamino
1154	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	9-methoxy
1155	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-methyl

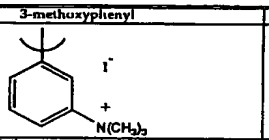
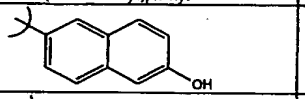
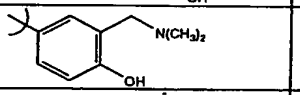
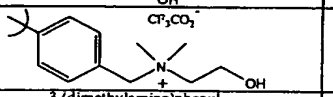
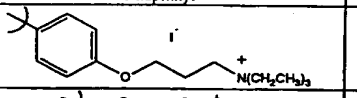
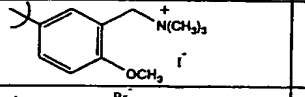
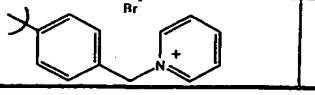
1156	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-methylmercapto
1157	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-fluoro; 9-dimethylamino
1158	n-butyl	n-butyl	OH	H	4-pyridinyl, hydrochloride salt	H	7-methoxy
1159	n-butyl	ethyl	OH	H	phenyl	H	7-dimethylamino
1160	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-diethylamino
1161	n-butyl	n-butyl	OH	H	3,5-dichloro-4-methoxyphenyl	H	7-dimethylamino
1162	n-butyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
1163	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl	H	7-methoxy
1164	n-butyl	n-butyl	OH	H	4-pyridinyl	H	7-methoxy
1165	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-trimethylammonium iodide
1166	n-butyl	n-butyl	OH	H	3-hydroxyphenyl	H	7-trimethylammonium iodide
1167	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1168	n-butyl	n-butyl	OH	H	4-hydroxyphenyl	H	7-trimethylammonium iodide
1169	n-butyl	n-butyl	OH	H	phenyl	H	8-dimethylamino
1170	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-ethylpropylamino
1171	n-butyl	n-butyl	OH	H	4-(trifluoromethylsulfonyloxy)phenyl	H	7-dimethylamino
1172	n-butyl	n-butyl	OH	H	4-pyridinyl	H	7-methoxy
1173	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-ethylpropylamino
1174	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-phenyl
1175	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-methylsulfonyl
1176	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-fluoro
1177	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-butylmethylamino
1178	n-butyl	n-butyl	OH	H	3-(trifluoromethylsulfonyloxy)phenyl	H	7-dimethylamino
1179	n-butyl	n-butyl	OH	H	phenyl	H	8-methoxy
1180	n-butyl	n-butyl	OH	H	phenyl	H	7-trimethylammonium iodide
1181	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-butylmethylamino
1182	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl	H	7-methoxy
1183	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-fluoro
1184	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-fluoro; 9-fluoro
1185	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-fluoro
1186	n-butyl	n-butyl	OH	H	phenyl	H	7-fluoro; 9-fluoro
1187	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-methyl
1188	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	7-trimethylammonium iodide
1189	n-butyl	n-butyl	OH	H	3,4-difluorophenyl	H	7-trimethylammonium iodide
1190	n-butyl	n-butyl	OH	H	2-bromophenyl	H	7-bromo
1191	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl	H	7-hydroxy
1192	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl	H	7-hydroxy
1193	n-butyl	n-butyl	OH	H	4-(2-(2-methylpropyl))phenyl	H	7-dimethylamino

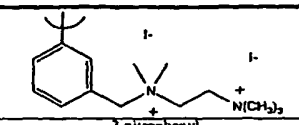
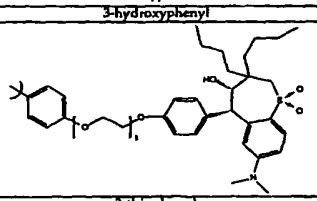
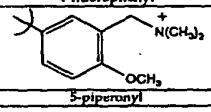
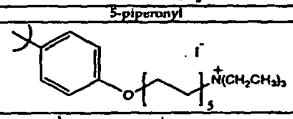
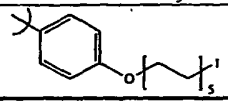
1194	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1195	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	7-(4'-methylpiperazin-1-yl)
1196	n-butyl	n-butyl	OH	H		H	7-methoxy
1197	n-butyl	ethyl	R3 + R4 = oxo	R3 + R4 = oxo	phenyl	H	7-(N-methylformamido)
1198	n-butyl	n-butyl	OH	H	4-(pyridinyl-N-oxide)	H	7-methoxy
1199	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1200	n-butyl	n-butyl	H	OH	H	phenyl	7-dimethylamino
1201	n-butyl	n-butyl	OH	H	H	H	7-methyl

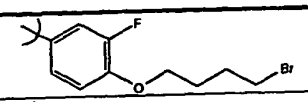
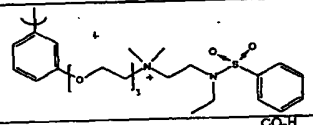
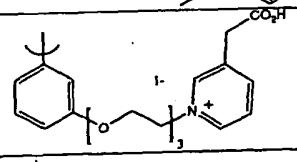
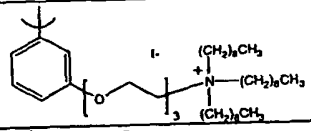
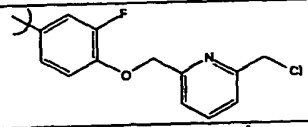
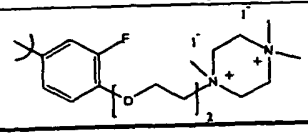
1202	n-butyl	n-butyl	OH	H		H	7-methoxy
1203	n-butyl	n-butyl	OH	H	5-piperazinyl	H	7-(4'-tert-butylphenyl)
1204	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-methoxy
1205	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1206	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1207	n-butyl	n-butyl	OH	H	3,5-dichlorophenyl	H	7-dimethylamino
1208	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	7-dimethylamino
1209	n-butyl	n-butyl	acetoxy	H	phenyl	H	7-dimethylphenyl
1210	n-butyl	n-butyl	OH	H	2-(dimethylamino)phenyl	H	7-dimethylamino
1211	ethyl	n-butyl	OH	H		H	7-dimethylamino
1212	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	9-(4'-morpholino)
1213	n-butyl	ethyl	H	OH	H	3-fluoro-4-methoxy-phenyl	7-dimethylamino
1214	n-butyl	ethyl	OH	H	phenyl	H	7-(N-methylformamido)
1215	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	9-methylmercapto

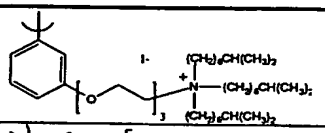
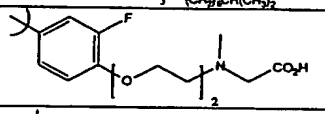
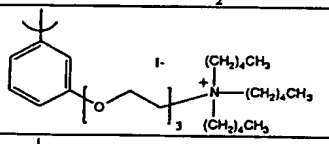
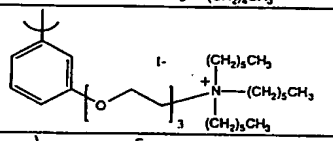
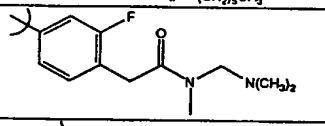
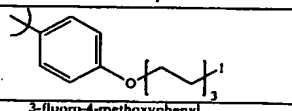
1216	ethyl	n-butyl	OH	H	5-piperonyl	H	7-bromo
1217	n-butyl	n-butyl	OH	H	4-carboxyphenyl	H	7-dimethylamino
1218	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	9-methylsulfonyl
1219	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1220	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-isopropylamino
1221	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1222	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-ethylamino
1223	n-butyl	n-butyl	OH	H	phenyl	H	8-bromo; 7-methylamino
1224	n-butyl	n-butyl	OH	H	3-nitrophenyl	H	7-fluoro
1225	n-butyl	ethyl	OH	H	3-methylphenyl	H	7-dimethylamino
1226	ethyl	n-butyl	OH	H	5-piperonyl	H	7-bromo
1227	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-(tert-butylamino
1228	n-butyl	n-butyl	OH	H	2-pyrrolyl	H	8-bromo; 7-dimethylamino
1229	n-butyl	n-butyl	OH	H	3-chloro-4-hydroxyphenyl	H	7-dimethylamino
1230	n-butyl	n-butyl	OH	H	phenyl	H	9-dimethylamino; 7-fluoro
1231	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1232	n-butyl	n-butyl	H	OH	3-thiophenyl	H	9-dimethylamino
1233	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1234	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1235	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1236	n-butyl	n-butyl	OH	H	4-(bromomethyl)phenyl	H	7-dimethylamino
1237	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1238	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1239	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1240	n-butyl	n-butyl	OH	H	4-methoxy-3-methylphenyl	H	7-dimethylamino
1241	n-butyl	n-butyl	OH	H	3-(dimethylaminomethyl)phenyl	H	7-dimethylamino
1242	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1243	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1244	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-(1'-methylhydrazido)
1245	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1246	n-butyl	n-butyl	OH	H	3-(bromomethyl)phenyl	H	7-dimethylamino
1247	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1248	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1249	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1250	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl	H	7-dimethylamino
1251	n-butyl	n-butyl	OH	H	1-naphthyl	H	7-dimethylamino
1252	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1253	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1254	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1255	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1256	n-butyl	n-butyl	OH	H	3-nitrophenyl	H	7-dimethylamino
1257	n-butyl	n-butyl	OH	H	phenyl	H	8-bromo; 7-dimethylamino
1258	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-(tert-butylamino)
1259	ethyl	n-butyl	H	OH	H	phenyl	7-dimethylamino
1260	ethyl	n-butyl	OH	H	3-hydroxyphenyl	H	7-dimethylamino
1261	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1262	n-butyl	n-butyl	OH	H	2-thiophenyl	H	7-dimethylamino
1263	n-butyl	n-butyl	OH	H	5-piperonyl	H	7-bromo
1264	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	7-isopropylamino
1265	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-isopropylamino
1266	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1267	n-butyl	ethyl	OH	H	5-piperonyl	H	7-carboxy, methyl ester
1268	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1269	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1270	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1271	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1272	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1273	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1274	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1275	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1276	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1277	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1278	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1279	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1280	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1281	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1282	ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-trimethylammonium iodide
1283	n-butyl	n-butyl	OH	H	4-hydroxymethylphenyl	H	7-dimethylamino
1284	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-ethylamino
1285	n-butyl	ethyl	OH	H	phenyl	H	7-dimethylamino

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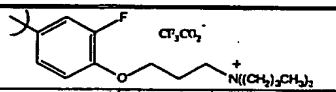
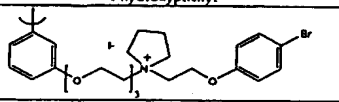
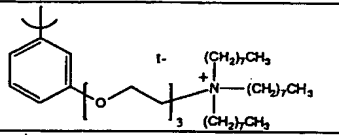
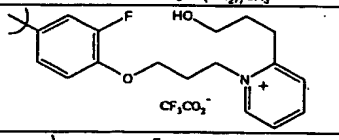
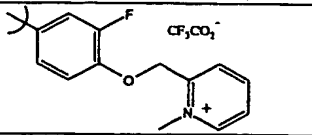
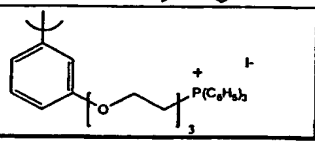
1286	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1287	n-butyl	ethyl	OH	H	4-hydroxyphenyl	H	7-dimethylamino
1288	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1289	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1290	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1291	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1292	n-butyl	n-butyl	OH	H		H	7-dimethylamnio

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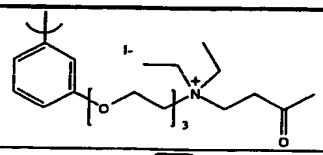
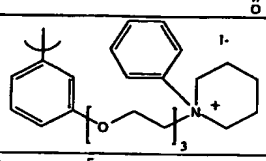
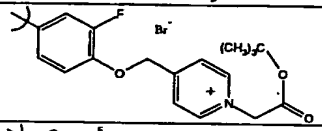
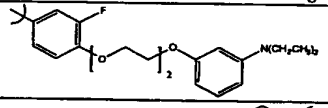
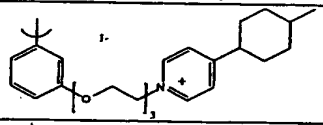
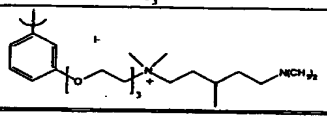
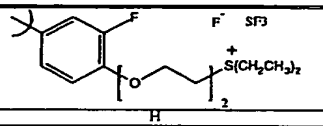
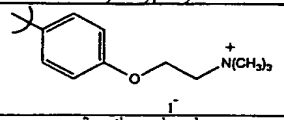
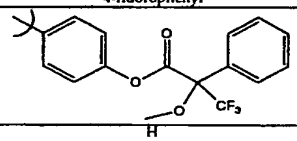
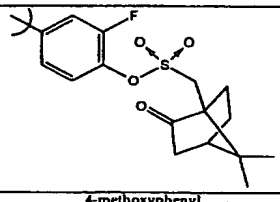
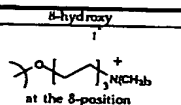
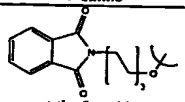
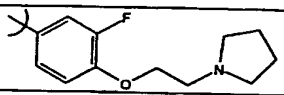
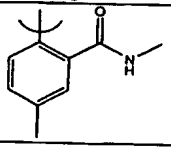
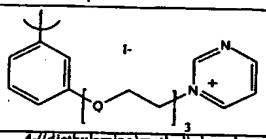
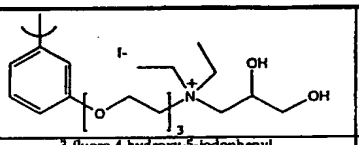
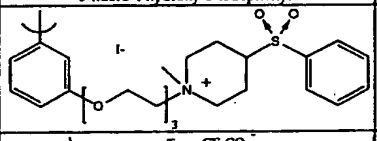
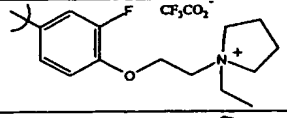
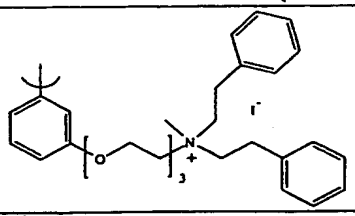
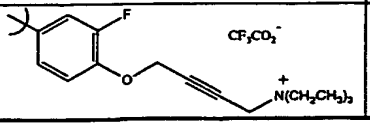
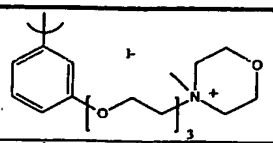
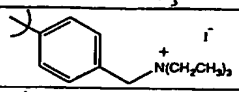
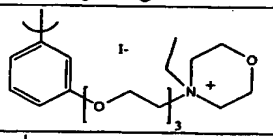
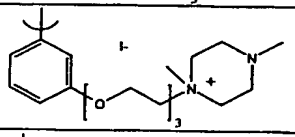
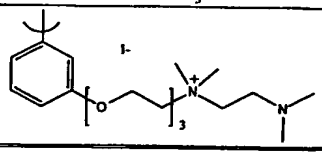
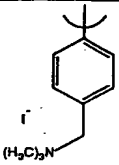
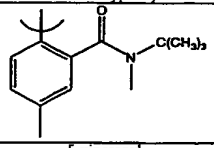
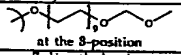
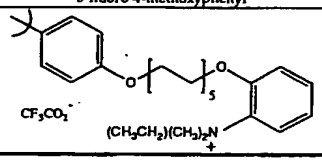
1293	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1294	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1295	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1296	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1297	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1298	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1299	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1300	n-butyl	ethyl	H	OH	H	phenyl	7-dimethylamino
1301	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-trimethylammonium iodide
1302	n-butyl	n-butyl	OH	H	3-hydroxyphenyl	H	9-hydroxy
1303	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1304	n-butyl	n-butyl	OH	H	3-methoxyphenyl	H	7-tert-butylamino
1305	n-butyl	n-butyl	OH	H	4-fluorophenyl	H	9-methylamino
1306	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1307	n-butyl	n-butyl	OH	H	H	4-methoxy-phenyl	9-(4'-morpholino)
1308	ethyl	n-butyl	OH	H		H	7-dimethylamino
1309	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	9-fluoro
1310	ethyl	n-butyl	OH	H	phenyl	H	7-amino
1311	n-butyl	ethyl	OH	H	phenyl	H	7-(hydroxylamino)
1312	n-butyl	ethyl	OH	H	phenyl	H	8-hexyloxy
1313	n-butyl	ethyl	OH	H	phenyl	H	8-ethoxy
1314	ethyl	n-butyl	OH	H	phenyl	H	7-(hydroxylamino)
1315	ethyl	n-butyl	OH	H	phenyl	H	7-(hexyloxy)

1316	n-butyl	ethyl	OH	H	phenyl	H	8-hydroxy
1317	n-butyl	ethyl	OH	H	phenyl	H	 at the 8-position
1318	ethyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
1319	ethyl	n-butyl	OH	H	3-methoxyphenyl	H	7-fluoro
1320	ethyl	n-butyl	OH	H	phenyl	H	7-amino
1321	n-butyl	ethyl	OH	H	phenyl	H	 at the 8-position
1322	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1323	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1324	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1325	n-butyl	n-butyl	OH	H	4-((diethylamino)methyl)phenyl	H	7-dimethylamino

1326	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1327	n-butyl	n-butyl	OH	H	3-fluoro-4-hydroxy-5-iodophenyl	H	7-dimethylamino
1328	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1329	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1330	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1331	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1332	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1333	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1334	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1335	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1336	n-butyl	n-butyl	OH	H		H	7-dimethylamino

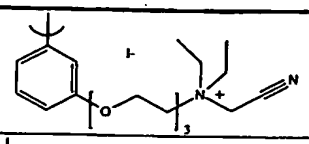
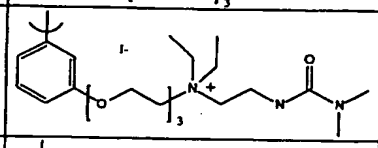
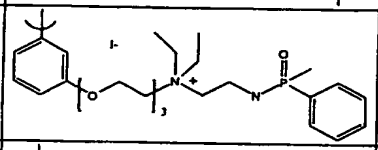
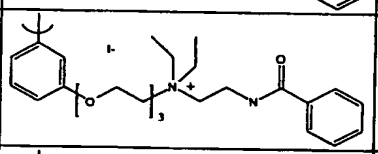
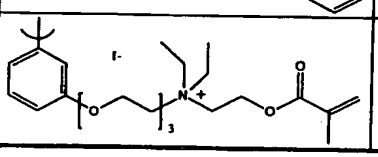
1337	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1338	n-butyl	n-butyl	OH	H	4-methoxyphenyl	H	7-(4'-methylpiperazinyl)
1339	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1340	n-butyl	ethyl	OH	H	5-piperonyl	H	7-methyl
1341	n-butyl	n-butyl	acetoxy	H	3-methoxyphenyl	H	7-dimethylamino
1342	n-butyl	n-butyl	OH	H	5-piperonyl	H	7-(4'-fluorophenyl)
1343	ethyl	n-butyl	OH	H	phenyl	H	7-amino
1344	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-dimethylamino
1345	ethyl	n-butyl	OH	H	phenyl	H	7-trimethylammonium iodide
1346	ethyl	n-butyl	OH	H	phenyl	H	 at the 8-position
1347	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-dimethylamino
1348	isobutyl	isobutyl	OH	H	phenyl	H	7-dimethylamino
1349	ethyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
1350	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl	H	7-trimethylammonium iodide
1351	n-butyl	n-butyl	OH	H		H	7-dimethylamino

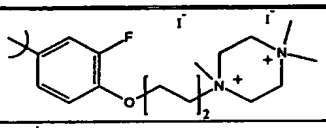
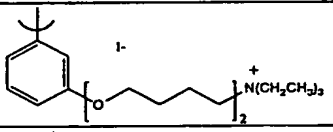
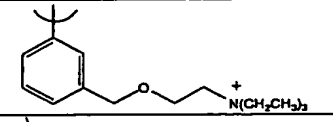
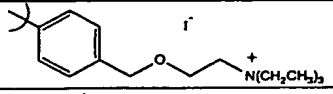
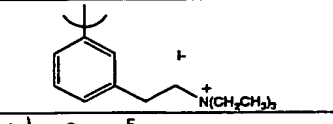
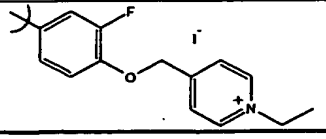
1352	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1353	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1354	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1355	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1356	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1357	n-butyl	n-butyl	OH	H		H	7-dimethylamino

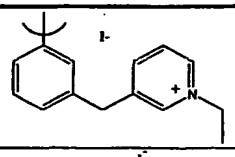
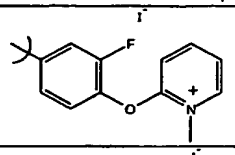
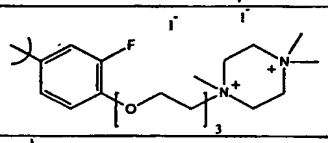
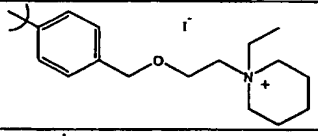
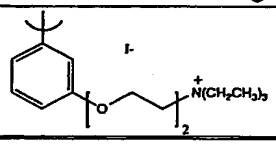
1358	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1359	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1360	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1361	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1362	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1363	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1364	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1365	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1366	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1367	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1368	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1369	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1370	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1371	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1372	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1373	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1374	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1375	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1376	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1377	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1378	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1379	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1380	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1381	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1382	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1383	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1384	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1385	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1386	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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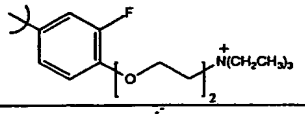
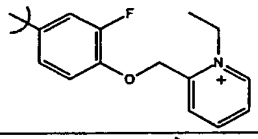
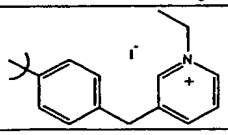
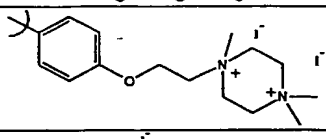
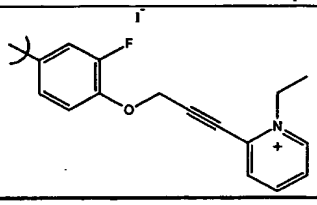
1387	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1388	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1389	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1390	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1391	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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1392	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1393	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1394	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1395	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1396	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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1397	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1398	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1399	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1400	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1401	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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1402	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1403	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1404	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1405	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1406	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1407	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1408	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1409	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1410	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1411	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1412	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1413	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1414	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1415	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1416	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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1417	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1418	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1419	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1420	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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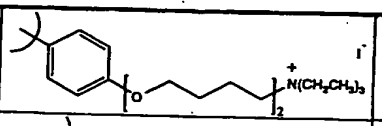
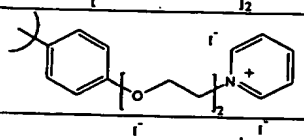
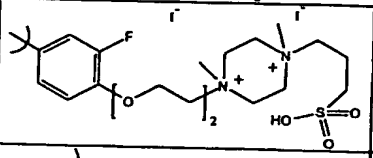
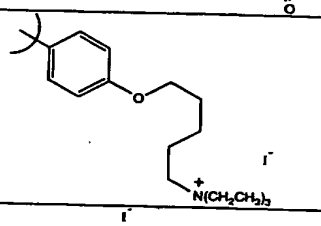
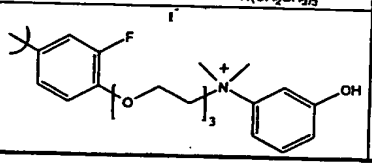
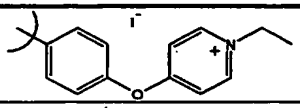
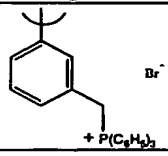
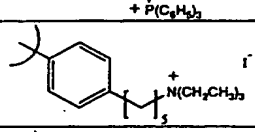
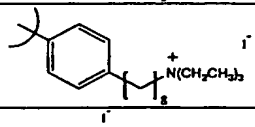
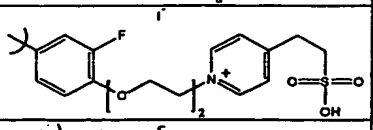
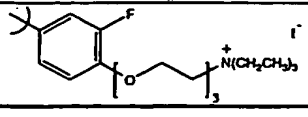
1421	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1422	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1423	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1424	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1425	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1426	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1427	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1428	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1429	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1430	n-butyl	n-butyl	OH	H		H	7-dimethylamino

1431	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1432	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1433	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1434	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1435	n-butyl	n-butyl	OH	H		H	7-dimethylamino

125

1436	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1437	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1438	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1439	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1440	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1441	n-butyl	n-butyl	OH	H		H	7-dimethylamino

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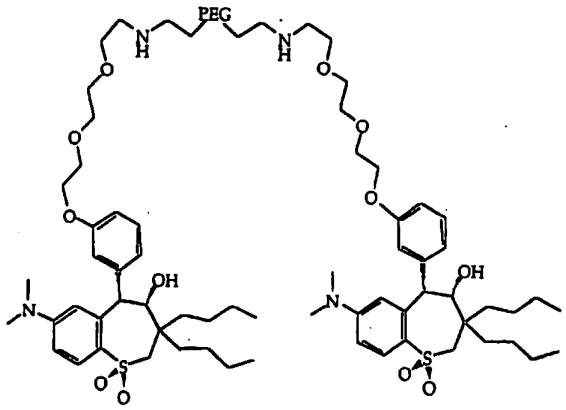
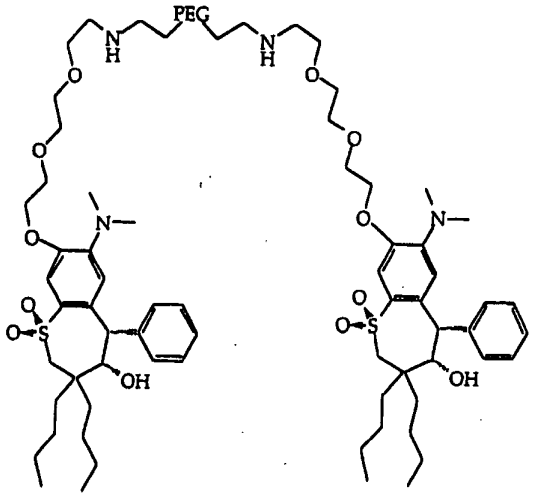
1442	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1443	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1444	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1445	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1446	n-butyl	n-butyl	OH	H		H	7-methoxy; 8-methoxy
1447	n-butyl	n-butyl	OH	H		H	7-dimethylamino

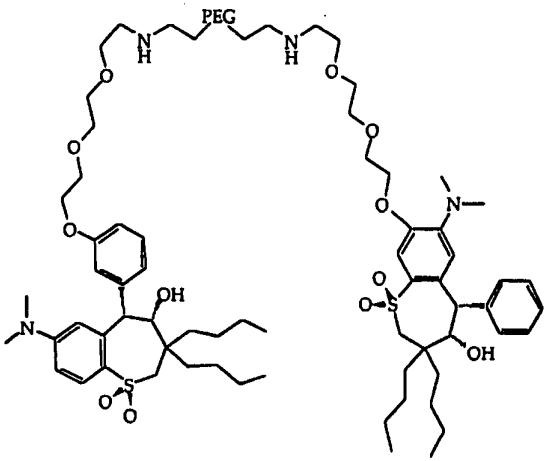
1448	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1449	n-butyl	n-butyl	OH	H		H	7-dimethylamino
1450	n-butyl	n-butyl	OH	H	phenyl	H	7-dimethylamino
1451	n-butyl	n-butyl	OH	H		H	7-dimethylamino



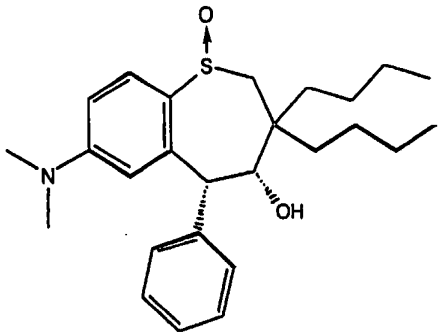
PEG = 3400 molecular weight polyethylene glycol polymer chain

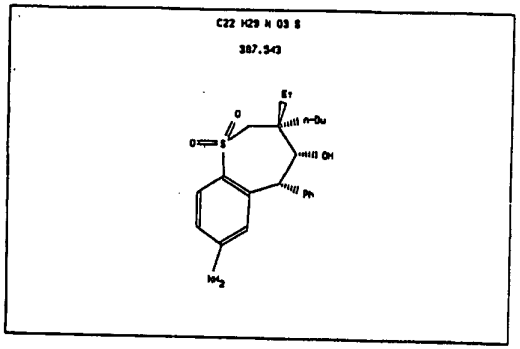


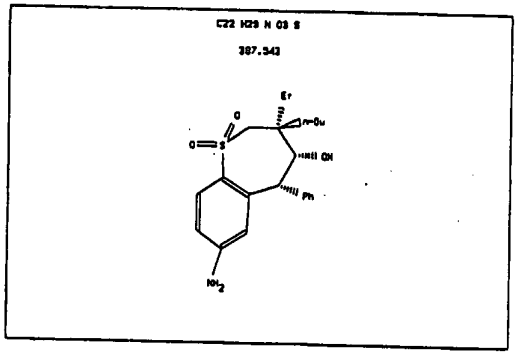
PEG = 3400 molecular weight polyethylene glycol polymer chain

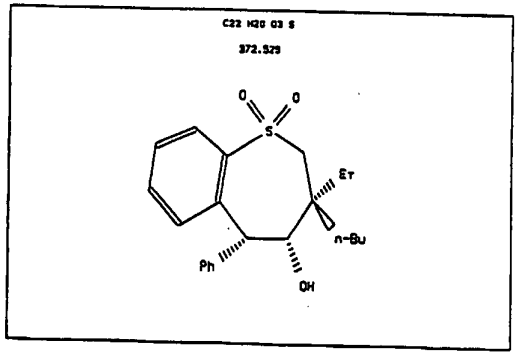


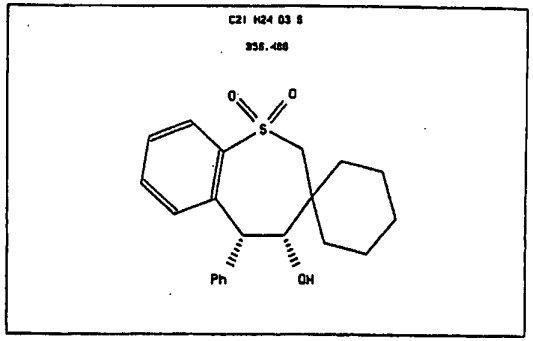
PEG = 3400 molecular weight polyethylene glycol polymer chain

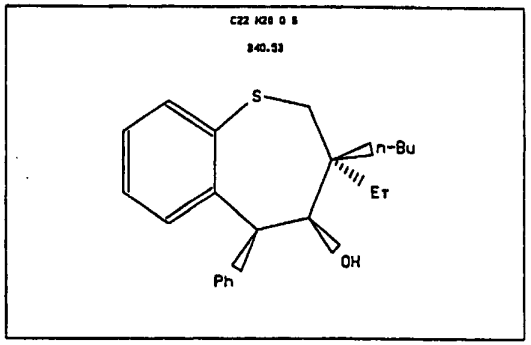


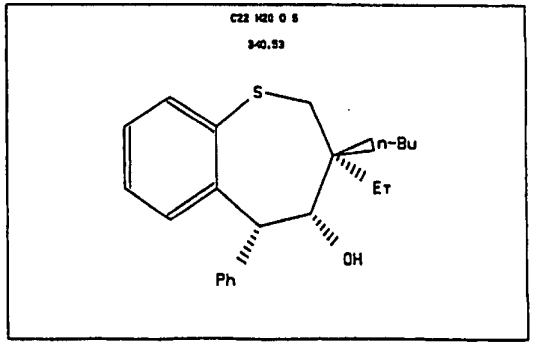

C22 H29 N 03 S
387.543
Et
n-Bu
OH
Ph
NH2

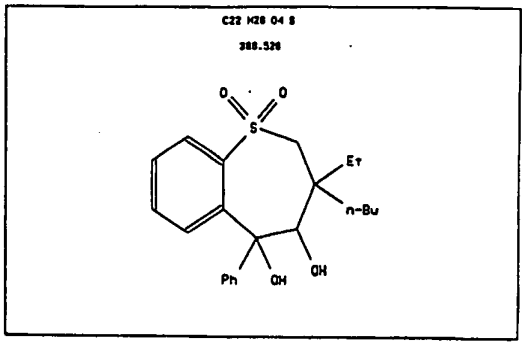

C22 H29 N 03 S
387.543
Et
n-Bu
OH
Ph
NH2

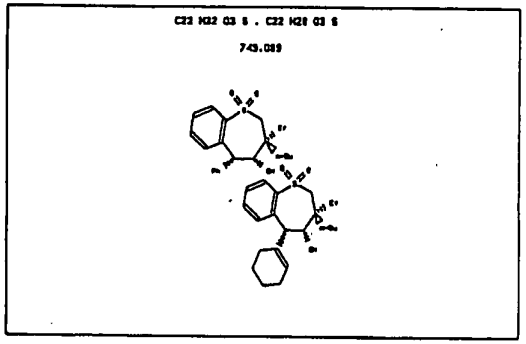

C22 H20 03 S
372.525
Et
n-Bu
Ph
OH

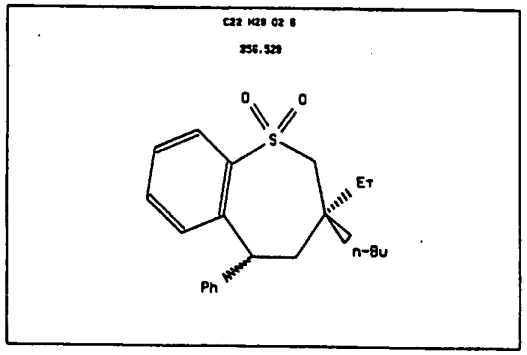

C21 H24 03 S
356.488
Ph
OH

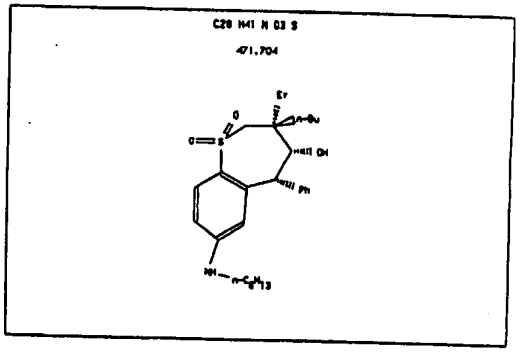

C22 H28 0 S
340.53
n-Bu
Et
Ph
OH

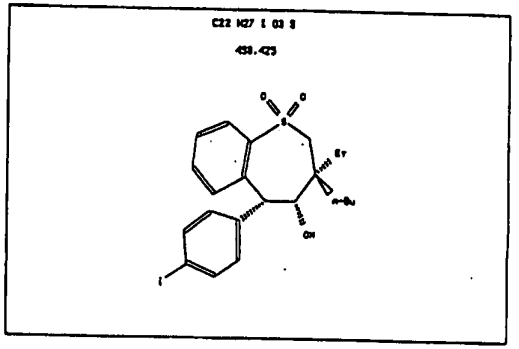

C22 H28 0 S
340.53
n-Bu
Et
Ph
OH

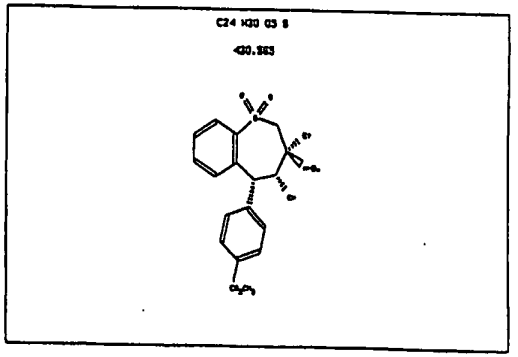

C22 H28 O4 S
388.526
O
O
S
Et
n-Bu
Ph
OH
OH

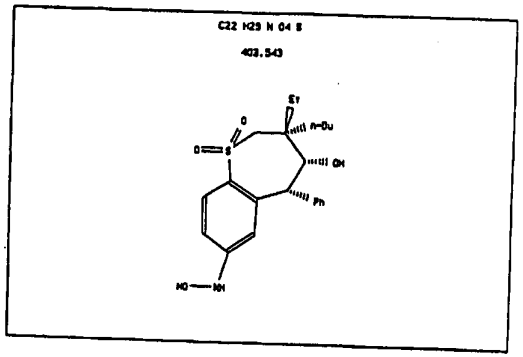

C22 H32 O3 S . C22 H28 O3 S
745.089

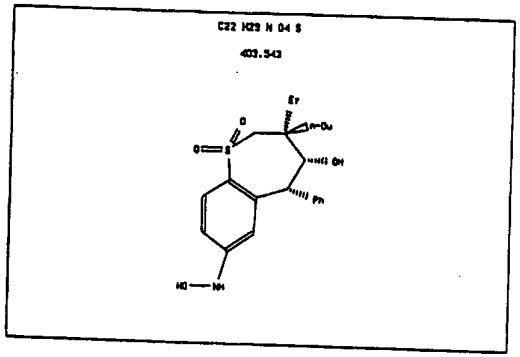

C22 H28 O2 S
356.529
O
O
S
Et
n-Bu
Ph

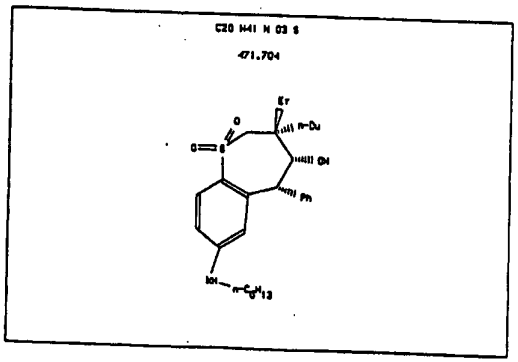

C28 H41 N O3 S
471.704

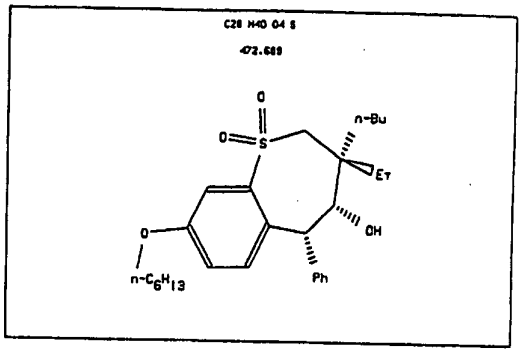

C22 H27 I O3 S
498.423
O
O
S
Et
n-Bu
OH
I

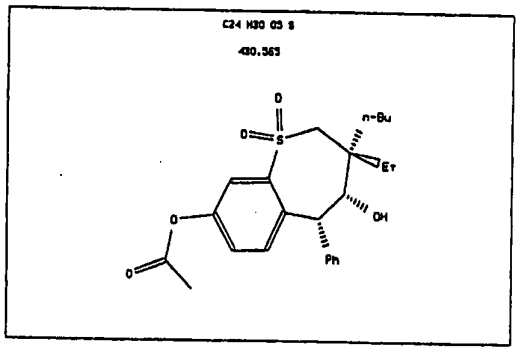

C24 H30 O3 S
430.563
O
O
S
Et
n-Bu
Ph

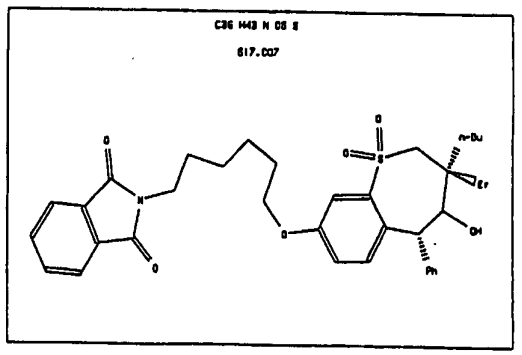

C22 H29 N 04 S
403.543
Et
n-Bu
OH
Ph
HO—NH

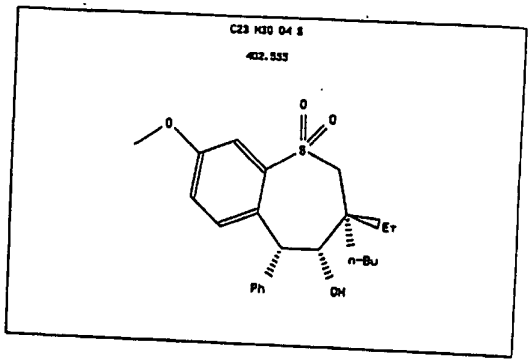

C22 H29 N 04 S
403.543
Et
n-Bu
OH
Ph
HO—NH

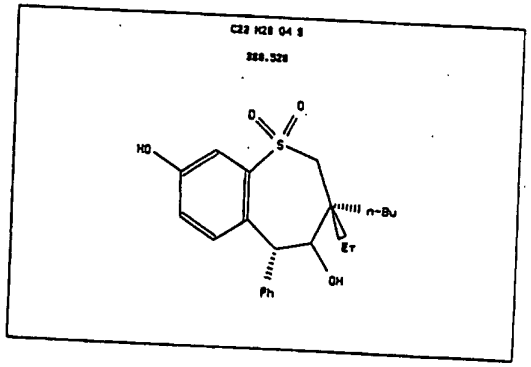

C28 H41 N 03 S
471.704
Et
n-Bu
OH
Ph
NH—n-C6H13

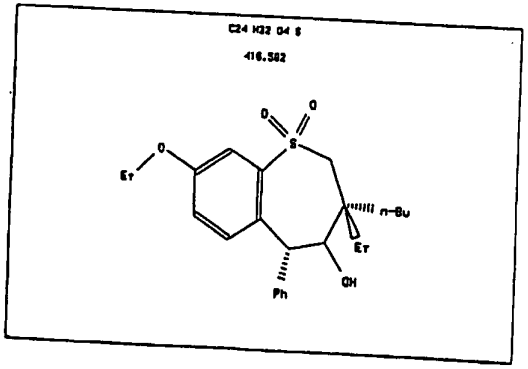

C28 H40 04 S
472.689
n-Bu
Et
OH
Ph
n-C6H13

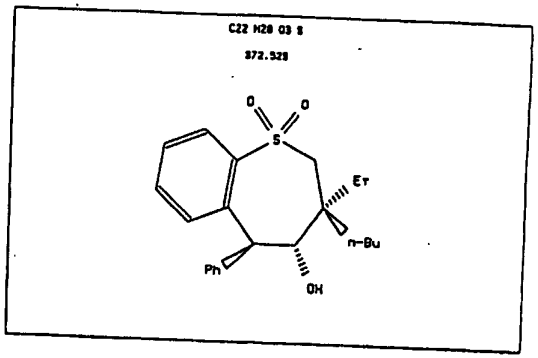

C24 H30 03 S
430.565
n-Bu
Et
OH
Ph

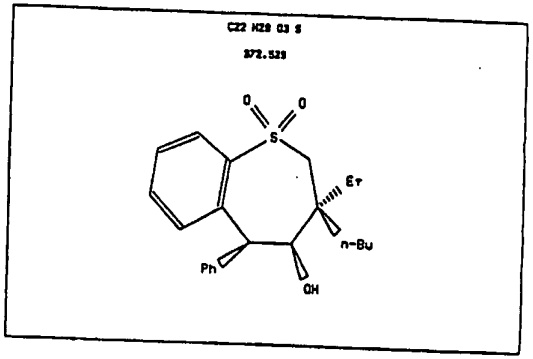

C36 H43 N 08 S
617.007
n-Bu
Et
OH
Ph

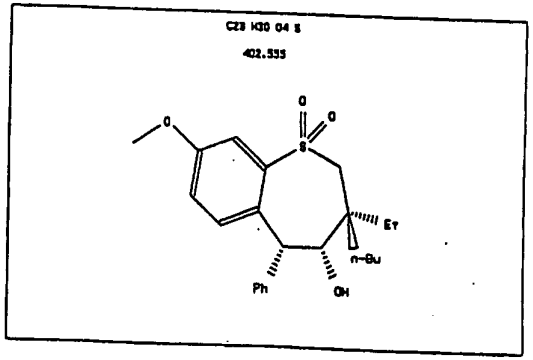

C23 H30 O4 S
402.555
O
O
S
O
Et
n-Bu
Ph
OH

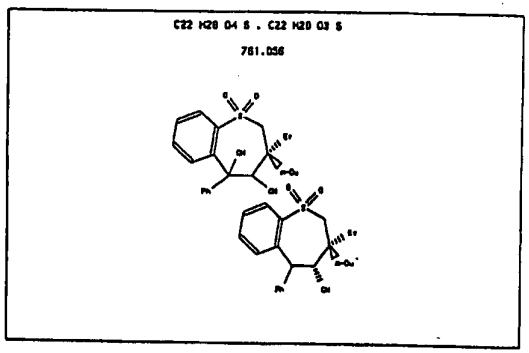

C22 H28 O4 S
388.528
HO
O
O
S
n-Bu
Et
Ph
OH

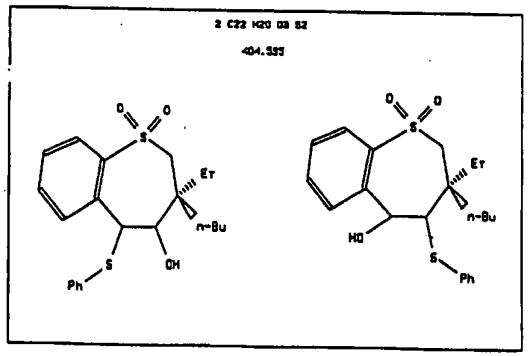

C24 H32 O4 S
416.582
O
O
S
O
Et
n-Bu
Et
Ph
OH


C22 H28 O3 S
372.528
O
O
S
Et
n-Bu
Ph
OH

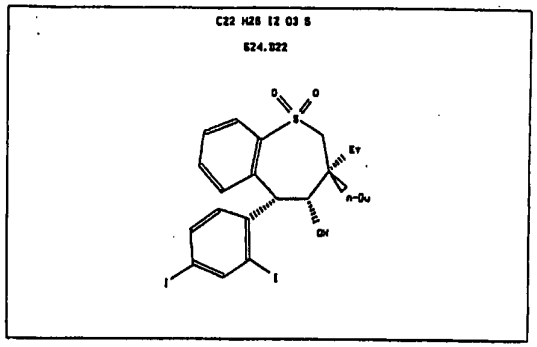

C22 H28 O3 S
372.528
O
O
S
Et
n-Bu
Ph
OH

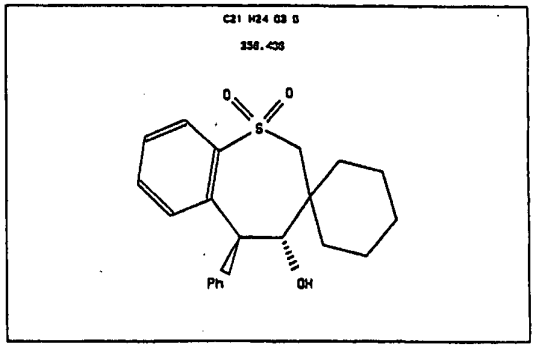

C23 H30 O4 S
402.555
O
O
S
O
Et
n-Bu
Ph
OH


C22 H28 O4 S . C22 H28 O3 S
781.056

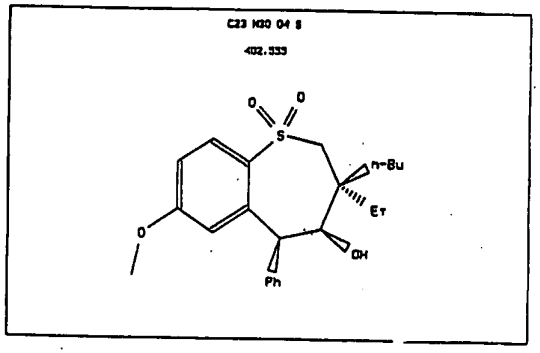

2 C22 H28 O3 S2
404.597
Et
n-Bu
OH
Ph
S
HO

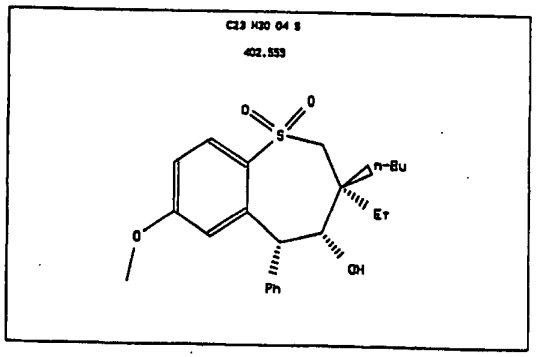
139


C22 H28 I2 O3 S
624.322
Et
n-Bu
OH
I

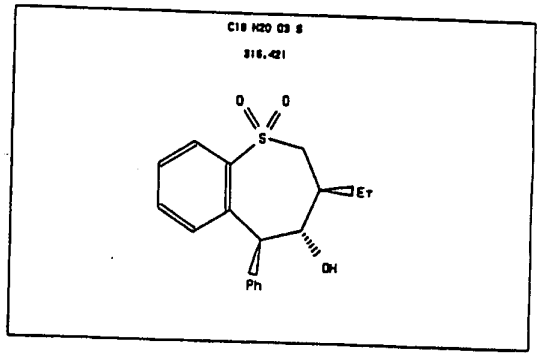

C21 H24 O3 S
356.436
Ph
OH

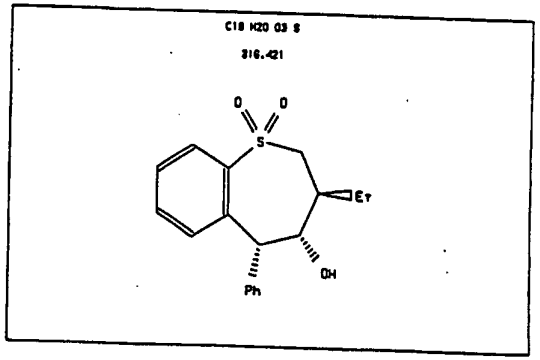
140


C23 H30 04 S
402.553
O
O
S
n-Bu
Et
O
OH
Ph

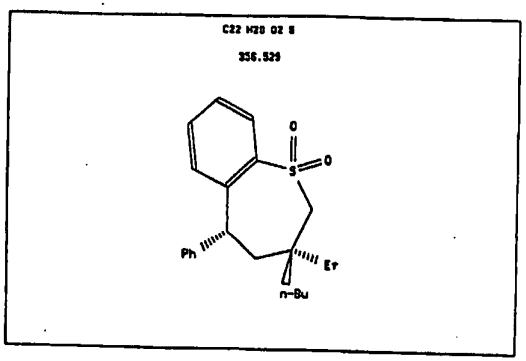

C23 H30 04 S
402.553
O
O
S
n-Bu
Et
O
OH
Ph

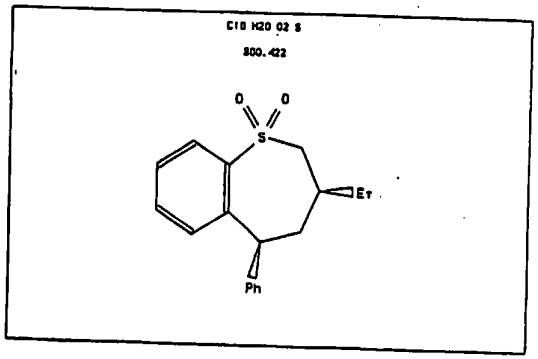
141

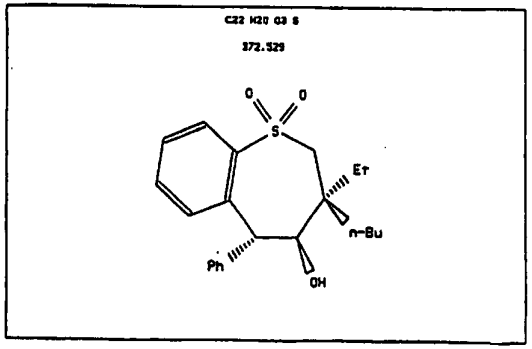

C18 H20 03 S
316.421
O
O
S
Et
OH
Ph


C18 H20 03 S
316.421
O
O
S
Et
OH
Ph

142







In further compounds of the present invention, R^5 and R^6 are independently selected from among hydrogen and ring-carbon substituted or unsubstituted aryl, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, pyrimidine, morpholine, N-alkylpyridinium, N-alkylpiperazinium, N-alkylmorpholinium, or furan in which the substituent(s) are selected from among halo, hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, N,N-dialkylamino, quaternary ammonium salts, a C_1 to C_4 alkylene bridge having a quaternary ammonium salt substituted thereon, alkoxycarbonyl, aryloxycarbonyl, alkylcarbonyloxy and arylcarbonyloxy, (O,O)-dioxyalkylene, $-[O(CH_2)_w]_xX$ where x is 2 to 12, w is 2 or 3 and X comprises halo or a quaternary ammonium salt, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, or furan. The aryl group of R^5 or R^6 is preferably phenyl, phenylene, or benzene triyl, i.e., may be unsubstituted, mono-substituted, or di-substituted. Among the species which may constitute the substituents on the aryl ring of R^5 or R^6 are fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, trimethylammonium (preferably with an iodide or chloride counterion), methoxycarbonyl, ethoxycarbonyl, formyl, acetyl, propanoyl, (N)-hexyldimethylammonium, hexylenetrimethylammonium, tri(oxyethylene)iodide, and tetra(oxyethylene)trimethyl-ammonium iodide, each substituted at the p-position, the m-position, or both of the aryl ring. Other substituents that can be present on a phenylene, benzene triyl or other aromatic ring include 3,4-dioxymethylene (5-membered ring) and

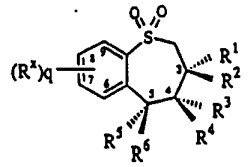
3,4-dioxyethylene (6- membered ring). Among compounds which have been or can be demonstrated to have desirable ileal bile acid transport inhibiting properties are those in which R^3 or R^4 is selected from phenyl, p-fluorophenyl, m-fluorophenyl, p-hydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, m-methoxyphenyl, p-N,N-dimethylaminophenyl, m-N,N-dimethylaminophenyl, I^- p-$(CH_3)_3$-N^+-phenyl, I^- m-$(CH_3)_3$-N^+-phenyl, I^- m-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-phenyl, I^- p-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-phenyl, I^- m-(N,N-dimethylpiperazinium)-(N')-CH_2-$(OCH_2CH_2)_2$-O-phenyl, 3-methoxy-4-fluorophenyl, thienyl-2-yl, 5-cholorothienyl-2-yl, 3,4-difluorophenyl, I^- p-(N,N-dimethylpiperazinium)-(N')-CH_2-$(OCH_2CH_2)_2$-O-phenyl, 3-fluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3-pyridinyl, N-methyl-4-pyridinium, I^- N-methyl-3-pyridinium, 3,4-dioxymethylenephenyl, 3,4-dioxyethylenephenyl, and p-methoxycarbonylphenyl. Preferred compounds include 3-ethyl-3-butyl and 3-butyl-3-butyl compounds having each of the above preferred R^3 substituents in combination with the R^4 substituents shown in Table 1. It is particularly preferred that one but not both of R^3 and R^4 is hydrogen.

It is especially preferred that R^4 and R^6 be hydrogen, that R^3 and R^5 not be hydrogen, and that R^3 and R^5 be oriented in the same direction relative to the plane of the molecule, i.e., both in a- or both in ß-configuration. It is further preferred that, where R^3 is butyl and R^1 is ethyl, then R^1 has the same

orientation relative to the plane of the molecule as R^3 and R^5.

Set forth in Table 1A are lists of species of R^1/R^3, R^5/R^4 and R^4.

Table 1A : Alternative R groups



R^1, R^2	R^3, R^4	R^5	$(R^x)q$
ethyl	HO-	Ph-	7-methyl
n-propyl	S-	p-F-Ph-	7-ethyl
n-butyl		m-F-Ph-	7-iso-propyl
n-pentyl		p-CH_3O-Ph-	7-tert-butyl
n-hexyl			7-OH
iso-propyl		m-CH_3O-Ph-	7-OCH_3
iso-butyl		p-$(CH_3)_2N$-Ph-	7-O(iso-propyl)
iso-pentyl		m-$(CH_3)_2N$-Ph-	7-SCH_3
$CH_2C(=O)C_2H_5$		I^-, p-$(CH_3)_3$-N^+-Ph-	7-$SOCH_3$
$CH_2OC_2H_5$		I^-, m-$(CH_3)_3$-N^+-Ph-	7-SO_2CH_3
$CH_2CH(OH)C_2H_5$		I^-, p-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-SCH_2CH_3
CH_2O-(4-picoline)		I^-, m-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-NH_2
		I^-, p-(N,N-dimethylpiperazine)-(N')-CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-NHOH
		I^-, m-(N,N-dimethylpiperazine)-(N')-CH_2-$(OCH_2CH_2)_2$-O-Ph-	7-$NHCH_3$
		m-F, p-CH_3O-Ph-	7-$N(CH_3)_2$
		3,4,dioxymethylene-Ph	7-$N^+(CH_3)_3$, I^-
		m-CH_3O-, p-F-Ph-	7-NHC(=O)CH_3
		4-pyridine	7-$N(CH_2CH_3)_2$
		N-methyl-4-pyridinium, I^-	7-$NMeCH_2CO_2H$
		3-pyridine	7-$N^+(Me)_2CH_2CO_2H$, I^-
		N-methyl-3-pyridinium, I^-	7-(N)-morpholine
		2-pyridine	7-(N)-azetidine
		p-CH_3O_2C-Ph-	7-(N)-N-methylazetidinium, I^-
		thienyl-2-yl	7-(N)-pyrrolidine
		5-Cl-thienyl-2-yl	7-(N)-N-methyl-pyrrolidinium, I^-
		3,4-difluoro	7-(N)-N-methyl-morpholinium, I^-
		m-F, p-CH_3O-Ph	7-(N)-N'-methylpiperazine
			7-(N)-N'-dimethylpiperazinium, I^-
			7-NH-CBZ
			7-$NHC(=O)C_5H_{11}$
			7-$NHC(=O)CH_2Br$
			7-NH-C(NH)NH_2
			7-(2)-thiophene

continued next page...

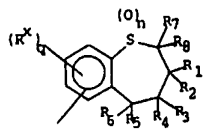
8-methyl
8-ethyl
8-iso-propyl
8-tert-butyl
8-OH
8-OCH_3
8-O(iso-propyl)
8-SCH_3
8-$SOCH_3$
8-SO_2CH_3
8-SCH_2CH_3
8-NH_2
8-NHOH
8-$NHCH_3$
8-$N(CH_3)_2$
8-$N^+(CH_3)_3$, I^-
8-NHC(=O)CH_3
8-$N(CH_2CH_3)_2$
8-$NMeCH_2CO_2H$
8-$N^+(Me)_2CH_2CO_2H$, I^-
8-(N)-morpholine
8-(N)-azetidine
8-(N)-N-methylazetidinium, I^-
8-(N)-pyrrolidine
8-(N)-N-methyl-pyrrolidinium, I^-
8-(N)-N-methyl-morpholinium, I^-
8-(N)-N'-methylpiperazine
8-(N)-N'-dimethylpiperazinium, I^-
8-NH-CBZ
8-$NHC(O)C_5H_{11}$
8-$NHC(O)CH_2Br$
8-NH-C(NH)NH_2
8-(2)-thiophene

continued next page...

9-methyl
9-ethyl
9-iso-propyl
9-tert-butyl
9-OH
9-OCH_3
9-O(iso-propyl)
9-SCH_3
9-$SOCH_3$
9-SO_2CH_3
9-SCH_2CH_3
9-NH_2
9-NHOH
9-$NHCH_3$
9-$N(CH_3)_2$
9-$N^+(CH_3)_3$, I^-
9-$NHC(=O)CH_3$
9-$N(CH_2CH_3)_2$
9-$NHmeCH_2CO_2H$
9-$N^+(Me)_2CH_2CO_2H$, I^-
9-(N)-morpholine
9-(N)-azetidine
9-(N)-N-methylazetidinium, I^-
9-(N)-pyrrolidine
9-(N)-N-methyl-pyrrolidinium, I^-
9-(N)-N-methyl-morpholinium, I^-
9-(N)-N'-methylpiperazine
9-(N)-N'-dimethylpiperazinium, I^-
9-NH-CBZ
9-$NHC(O)C_5H_{11}$
9-$NHC(O)CH_2Br$
9-NH-C(NH)NH_2
9-(2)-thiophene

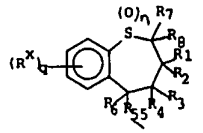
7-OCH_3, 8-OCH_3
7-SCH_3, 8-OCH_3
7-SCH_3, 8-SCH_3
6-OCH_3, 7-OCH_3, 8-OCH_3

Further preferred compounds of the present invention comprise a core structure having two or more pharmaceutically active benzothiepine structures as described above, covalently bonded to the core moiety via functional linkages. Such active benzothiepine structures preferably comprise:



(Formula DIV)

or:



(Formula DIVA)

where R^1, R^2, R^3, R^4, R^6, R^5, R^4, R^7, R^8, X, q and n are as defined above, and R^{55} is either a covalent bond or arylene.

The core moiety can comprise alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR', N+R'R', S, SO, SO2, S+R'R', PR7, P+R7R8, phenylene, heterocycle, quatarnary heterocycle, quaternary heteroaryl, or aryl,

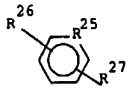
wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$;

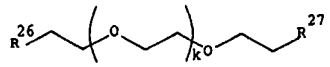
wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and P(O)(OR')OR', and

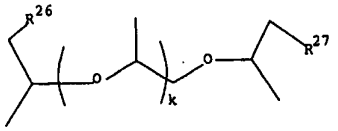
wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O,

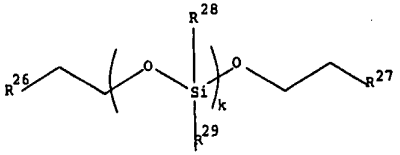
NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, P(O)R', $P^+R^7R^8A^-$, or phenylene.

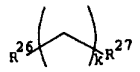
Exemplary core moieties include:







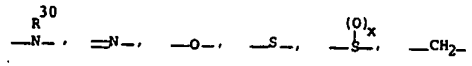


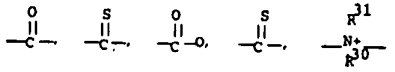


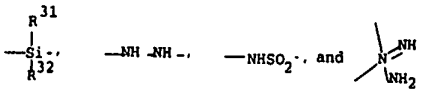
wherein:

R^{25} is selected from the group consisting of C and N, and

R^{28} and R^{29} are independently selected from the group consisting of:







wherein R^{26}, R^{29}, R^{30} and R^{31} are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

A^- is a pharmaceutically acceptable anion, and k = 1 to 10.

In compounds of Formula DIV, R^{20}, R^{21}, R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII can be bonded at any of their 6-, 7-, 8-, or 9- positions to R^{19}. In compounds of Formula DIVA, it is preferred that R^{19} comprises a phenylene moiety bonded at a m- or p-position thereof to R^{19}.

In another embodiment, a core moiety backbone, R^{19}, as discussed herein in Formulas DII and DIII can be multiply substituted with more than four pendant active benzothiepine units, i.e., R^{20}, R^{21}, R^{22}, and R^{23} as discussed above, through multiple functional groups within the core moiety backbone. The core moiety backbone unit, R^{19}, can comprise a single core moiety unit, multimers thereof, and multimeric mixtures of the different core moiety units discussed herein, i.e., alone or in combination. The number of individual core

moiety backbone units can range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. The number of points of attachment of similar or different pendant active benzothiepine units within a single core moiety backbone unit can be in the range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. Such points of attachment can include bonds to C, S, O, N, or P within any of the groups encompassed by the definition of R^{19}.

The more preferred benzothiepine moieties comprising R^{20}, R^{21}, R^{22} and/or R^{23} conform to the preferred structures as outlined above for Formula I. The 3-carbon on each benzothiepine moiety can be achiral, and the substituents R^1, R^2, R^3, R^4, R^5 and R^6 can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(exyalkylene) or oligo(oxyalkylene), especially poly- or oligo(exyethylene) or poly- or oligo(oxypropylene).

Dosages, Formulations, and Routes of Administration

The ileal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of action in the body, for example in the ileum of a mammal, e.g., a human.

For the prophylaxis or treatment of the conditions referred to above, the compounds of the present invention can be used as the compound *per se*.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a

pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, and alkaline earth salts such as magnesium and calcium salts.

The anions of the definition of A in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

The compounds of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

These compounds can be administered by any conventional means available for use in conjunction

with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

The amount of compound which is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

In general, a daily dose can be in the range of from about 0.3 to about 100 mg/kg bodyweight/day, preferably from about 1 mg to about 50 mg/kg bodyweight/day, more preferably from about 3 to about 10 mg/kg bodyweight/day. This total daily dose can be administered to the patient in a single dose, or in proportionate multiple subdoses. Subdoses can be administered 2 to 6 times per day. Doses can be in sustained release form effective to obtain desired results.

Orally administrable unit dose formulations, such as tablets or capsules, can contain, for example, from about 0.1 to about 100 mg of benzothiepine compound, preferably about 1 to about 75 mg of compound, more preferably from about 10 to about 50 mg of compound. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiepine ion derived from the salt.

Oral delivery of an ileal bile acid transport inhibitor of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time

period over which the active drug molecule is delivered to the site of action (the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

When administered intravenously, the dose can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one

compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood.

Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

The solid dosage forms for oral administration including capsules, tablets, pills, powders, and

granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Pharmaceutically acceptable carriers encompass all the foregoing and the like.

Treatment Regimen

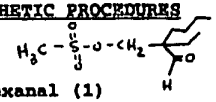
The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or

to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

Initial treatment of a patient suffering from a hyperlipidemic condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic disease condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum cholesterol levels by any of the methods well known in the art, to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of compounds of the present invention are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of ileal bile acid transport inhibitor of the present invention which exhibits satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the hyperlipidemic condition.

The following non-limiting examples serve to illustrate various aspects of the present invention.

EXAMPLES OF SYNTHETIC PROCEDURES


(1)

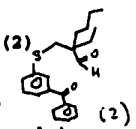
Preparation 1

2-Ethyl-2-(mesyloxymethyl)hexanal (1)

To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of triethylamine was added dropwise 15.8 g of 2-ethyl-2-(hydroxymethyl)hexanal, prepared according to the procedure described in Chem. Ber. 98, 728-734 (1965), while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with dilute HCl and extracted with methlyene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give 24.4 g of brown oil.

Preparation 2

2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

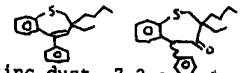

(2)

A mixture of 31 g (0.144 mol) of 2-mercaptobenzophenone, prepared according to the procedure described in WO 93/16055, 24.4 g (0.1 mole) of 2-ethyl-2-(mesyloxymethyl)-hexanal (1), 14.8 g (0.146 mole) of triethylamine, and 80 mL of 2-methoxyethyl ether was held at reflux for 24 h. The reaction mixture was poured into 3N HCl and extracted

with 300 mL of methylene chloride. The methylene chloride layer was washed with 300 mL of 10% NaOH, dried over $MgSO_4$ and concentrated in vacuo to remove 2-methoxyethyl ether. The residue was purified by HPLC (10% EtOAc-hexane) to give 20.5 g (58%) of **2** as an oil.

Example 1

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine (3), *cis*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5*H*)4-one (4a) and *trans*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5*H*)4-one (4b)

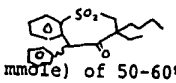


4a, 4b

A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_4$ and 80 mL of anhydrous ethylene glycol dimethyl ether (DME) was held at reflux for 2 h. The reaction mixture was cooled to 5 °C. To the reaction mixture was added dropwise a solution of 3.54 g (0.01 mole) of **2** in 30 mL of DME in 40 min. The reaction mixture was stirred at room temperature for 16 h and then was held at reflux for 2 h and cooled before being poured into brine. The organic was extract into methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (hexane) to give 1.7 g (43%) of **3** as an oil in the first fraction. The second fraction was discarded and the third fraction was further purified by HPLC (hexane) to give 0.07 g (2%) of **4a** in the earlier fraction and 0.1 g (3%) of **4b** in the later fraction.

Example 2

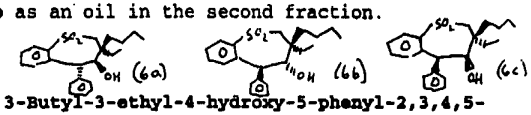
cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5*H*)4-one-1,1-dioxide (5a) and _trans_-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5*H*)4-one-1,1-dioxide (5b)



5a, 5b

To a solution of 1.2 g (3.5 mmole) of 50-60% MCPBA in 20 mL of methylene chloride was added 0.59 g (1.75

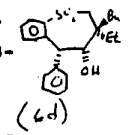
mmole) of a mixture of **4a** and **4b** in 10 mL of methylene chloride. The reaction mixture was stirred for 20 h. An additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added and the reaction mixture was stirred for an additional 3 h then was triturated with 50 mL of 10% NaOH. The insoluble solid was filtered. The methylene chloride layer of the filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual syrup was purified by HPLC (5% EtOAc-hexane) to give 0.2 g (30%)of **5a** as an oil in the first fraction and 0.17 g (26%) of **5b** as an oil in the second fraction.



(6a) (6b) (6c)

Example 3

(3a,4a,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6a), (3a,4b,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (6b), (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)



(6d)

A. Reduction of 5a and 5b with Sodium Borohydride

To a solution of 0.22 g (0.59 mmole) of **5b** in 10 mL of ethanol was added 0.24 g (6.4 mmole) of sodium borohydride. The reaction mixture was stirred at room temperature for 18 h and concentrated in vacuo to remove ethanol. The residue was triturated with water and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give 0.2 g of syrup. In a separate experiment, 0.45 g of **5a** was treated with 0.44 g of sodium borohydride in 10 mL of ethanol and was worked up as described above to give 0.5 g of syrup which was identical to the 0.2 g of syrup obtained above. These two materials were combined and purified by HPLC using 10% EtOAc-hexane as eluant. The first fraction was 0.18 g (27%) of **6a** as a syrup. The second fraction was 0.2 g

(30%) of **6b** also as a syrup. The column was then eluted with 20% EtOAc-hexane to give 0.077 g (11%) of **6c** in the third fraction as a solid. Recrystallization from hexane gave a solid, mp 179-181 °C. Finally, the column was eluted with 30% EtOAc-hexane to give 0.08 g (12%) of **6d** in the fourth fraction as a solid. Recrystallization from hexane gave a solid, mp 160-161 °C.

B. Conversion of 6a to 6c and 6d with NaOH and PTC

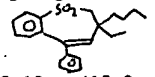
To a solution of 0.29 g (0.78 mmole) of **6a** in 10 mL CH_2Cl_2, was added 9 g of 40% NaOH. The reaction mixture was stirred for 0.5 h at room temperature and was added one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst (PTC). The mixture was stirred for 0.5 h at room temperature before being treated with 25 mL of ice-crystals then was extracted with CH_2Cl_2 (3x10 ml), dried over $MgSO_4$ and concentrated in vacuo to recover 0.17 g of a colorless film. The components of this mixture were separated using an HPLC and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2-(2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the first fraction, 30.9 mg (11%) of **6c** in the second fraction and 90.0 mg (31%) of **6d** in the third fraction.

Oxidation of 6a to 5b

To a solution of 0.20 g (0.52 mmole) of **6a** in 5 mL of CH_2Cl_2 was added 0.23 g (1.0 mmole) of pyridinium chlorochromate. The reaction mixture was stirred for 2 h then was treated with additional 0.23 g of pyridinium chlorochromate and stirred overnight. The dark reaction mixture was poured into a ceramic filterfrit containing silica gel and was eluted with CH_2Cl_2. The filtrate was concentrated in vacuo to recover 167 mg (87%) of **5b** as a colorless oil.

Example 4

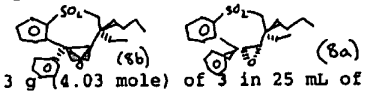
3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-dioxide (7)



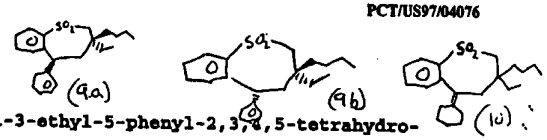
To a solution of 5.13 g (15.9 mmole) of **3** in 50 mL of CH_2Cl_2 was added 10 g (31.9 mmole) of 50-60% MCPBA (m-chloroperoxybenzoic acid) portionwise causing a mild reflux and formation of a white solid. The reaction mixture was allowed to stir overnight under N_2 and was triturated with 25 mL of water followed by 50 mL of 10% NaOH solution. The organic was extracted into CH_2Cl_2 (4x20 mL). The CH_2Cl_2 extract was dried over $MgSO_4$ and evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

Example 5

(1aa,2b,8ba) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (8a) (1aa,2a,8ba) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino [4,5-*b*]oxirene-4,4-dioxide (8b)



To 1.3 g (4.03 mole) of **3** in 25 mL of $CHCl_3$ was added portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a mild exotherm. The reaction mixture was stirred under N_2 overnight and was then held at reflux for 3 h. The insoluble white slurry was filtered. The filtrate was extracted with 10% potassium carbonate (3x50 mL), once with brine, dried over $MgSO_4$, and concentrated in vacuo to give 1.37 g of a light yellow oil. Purification by HPLC gave 0.65 g of crystalline product. This product is a mixture of two isomers. Trituration of this crystalline product in hexane recovered 141.7 mg (10%) of a white crystalline product. This isomer was characterized by NMR and mass spectra to be the (1aa,2b,8ba) isomer **8a**. The hexane filtrate was concentrated in vacuo to give 206 mg of white film which is a mixture of 30% **8a** and 70% **8b** by ^1H NMR.



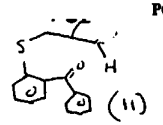
Example 6

cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (9a), trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (9b), and 3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidine-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (10)

A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of **8a** and **8b** was dissolved in 15 ml MeOH in a 3 oz. Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C catalyst. This mixture was hydrogenated at 70 psi H_2 for 5 h and filtered. The filtrate was evaporated to dryness in vacuo to recover 0.117 g of a colorless oil. This material was purified by HPLC eluting with EtOAc-hexane. The first fraction was 4.2 mg (3%) of **9b**. The second fraction, 5.0 mg (4%), was a 50/50 mixture of **9a** and **9b**. The third fraction was 8.8 mg (6%) of **6a** . The fourth fraction was 25.5 mg (18%) of **6b**. The fifth fraction was 9.6 mg (7%) of a mixture of **6b** and a product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide based on mass spectrum. The sixth fraction was 7.5 mg (5%) of a mixture of **6d** and one of the isomers of **10**, **10a**.

Example 7

In another experiment, a product (3.7 g) from epoxidation of **3** with excess MCPBA in refluxing $CHCl_3$ under air was hydrogenated in 100 mL of methanol using 1 g of 10% Pd/C catalyst and 70 psi hydrogen. The product was purified by HPLC to give 0.9 g (25%) of **9b**, 0.45 g (13%) of **9a**, 0.27 g (7%) of **6a**, 0.51 g (14%) of **6b**, 0.02 g (1%) of **6c**, 0.06 g (2%) of one isomer of **10**, **10a** and 0.03 g (1%) of another isomer of **10**, **10b**.



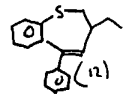
Example 8

2-((2-Benzoylphenylthio)methyl)butyraldehyde (11)

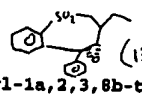
To an ice bath cooled solution of 9.76 g (0.116 mole) of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g (0.116 mole) of 2-mercaptobenzophenone in 40 mL of THF followed by 13 g (0.128 mole) of triethylamine. The reaction mixture was stirred at room temperature for 3 days , diluted with ether, and was washed successively with dilute HCl, brine, and 1 M potassium carbonate. The ether layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc-hexane) to give 22 g (64%) of **11** in the second fraction. An attempt to further purifiy this material by kugelrohr distillation at 0.5 torr (160-190 °C) gave a fraction (12.2 g) which contained starting material indicating a reversed reaction during distillation. This material was dissolved in ether (100 mL) and was washed with 50 mL of 1 M potassium carbonate three times to give 6.0 g of a syrup which was purified by HPLC (10% EtOAc-hexane) to give 5.6 g of pure **11**.

Example 9

3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine (12)



To a mixture of 2.61 g (0.04 mole) of zinc dust and 60 mL of DME was added 7.5 g (0.048 mole) of $TiCl_4$. The reaction mixture was held at reflux for 2 h. A solution of 2.98 g (0.01 mole) of **11** was added dropwise in 1 h. The reaction mixture was held at reflux for 18 h, cooled and poured into water. The organic was extracted into ether. The ether layer was washed with brine and filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated. The residual oil (2.5 g) was purified by HPLC to give 2.06 g (77%) of **12** as an oil in the second fraction.



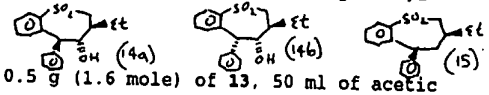
Example 10

(1aa,2a,8ba) 2-Ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino-[4,5-*b*]oxirene-4,4-dioxide (13)

To a solution of 1.5 g (5.64 mmole) of **12** in 25 ml of $CHCl_3$ was added 6.8 g (19.4 mmole) of 50-60% MCPB portionwise causing an exothem and formation of a white solid. The mixture was stirred at room temperature overnight diluted with 100 ml methylene chloride and washed successively with 10% K_2CO_3 (4x50 ml), water (twice with 25 ml) and brine. The organic layer was then dried over $MgSO_4$ and evaporated to dryness to recover 1.47 g of an off white solid. ^1H NMR indicated that only one isomer is present. This solid was slurried in 200 ml of warm Et_2O and filtered to give 0.82 g (46%) of **13** as a white solid, mp 185-186.5 °C.

Example 11

(3a,4b,5a)- 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (14a), (3a,4b,5b) 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (14b), and cis-3-Ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (15)

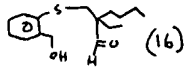


A mixture of 0.5 g (1.6 mole) of **13**, 50 ml of acetic acid and 0.5 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 4 h. The crude reaction slurry was filtered and the filtrate was stirred with 150 ml of a saturated $NaHCO_3$ solution followed by 89 g of $NaHCO_3$ powder portionwise to neutralize the rest of acetic acid. The mixture was extracted with methylene chloride (4x25 ml), then the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 0.44 g (87%) of a voluminous white solid which was purified by HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of **15** in the first fraction, 272 mg (54%) of **14a** as a solid, mp 142-

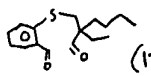
143.5 °C, in the second fraction, and 35 mg (7%) of impure **14b** in the third fraction.

Example 12

2-Ethyl-2-((2-Hydroxymethylphenyl)thiomethyl)hexenal (16)



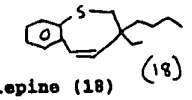
A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl alcohol, 6.4 g (0.032 mole) of **1**, 3.6 g (0.036 mole) of triethylamine and 25 mL of 2-methoxyethyl ether was held at reflux for 7 h. Additional 1.1 g of mercaptobenzyl alcohol and 0.72 g of triethylamine was added to the reaction mixture and the mixture was held at reflux for additional 16 h. The reaction mixture was cooled and poured into 6N HCl and extracted with methylene chloride. The methylene chloride extract was washed twice with 10% NaOH, dried over $MgSO_4$ and concentrated in vacuo to give 9.6 g of residue. Purification by HPLC (20% EtOAc-hexane) gave 3.7 g (41%)of **16** as an oil.



Example 13

2-Ethyl-2-((2-formylphenyl)thiomethyl)hexenal (17)

A mixture of 3.7 g of **16**, 5.6 g (0.026 mole) of pyridinium chlorochromate, 2 g of Celite and 30 mL of methylene chloride was stirred for 18 h and filtered through a bed of silica gel. The silica gel was eluted with methylene chloride. The combined methylene chloride eluant was purified by HPLC (20% ETOAc-hexane) to give 2.4 g (66%) of an oil.



Example 14

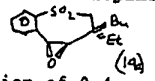
3-Butyl-3-ethyl-2,3-dihydrobenzothiepine (18)

A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_4$, and 50 mL of DME was held at

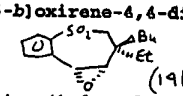
reflux for 2 h and cooled to room temperature. To this mixture was added 2.4 g (8.6 mmole) of **17** in 20 mL of DME in 10 min. The reaction mixture was stirred at room temperature for 2 h and held at reflux for 1 h then was let standing at room temperature over weekend. The reaction mixture was poured into dilute HCl and was stirred with methylene chloride. The methylene chloride-water mixture was filtered through Celite. The methylene chloride layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 3.0 g of a residue. Purification by HPLC gave 0.41 g (20%) of **18** as an oil in the early fraction.

Example 15

(1aa,2a,8ba) 2-Butyl-2-ethyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide (19a) and (1aa,2b,8ba) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide (19b)



(19a)



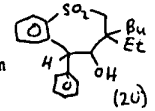
(19b)

To a solution of 0.4 g of 0.4 g (1.6 mmole) of **18** in 30 mL of methylene chloride was added 2.2 g (3.2 mmole) of 50-60% MCPBA. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was dissolved in 30 mL of $CHCl_3$ and was held at reflux for 18 h under N_2. The reaction mixture was stirred with 100 mL of 10% NaOH and 5 g of sodium sulfite. The methylene chloride layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (20% EtOAc-hexane) to give a third fraction which was further purified by HPLC (10% EtOAc-hexane) to give 0.12 g of syrup in the first fraction.
Recrystallization from hexane gave 0.08 g (17%) of **19a**, mp 89.5-105.5 °C. The mother liquor from the first fraction was combined with the second fraction and was further purified by HPLC to give additional **19a** in the first fraction and 60 mg of **19b** in the second fraction.

Crystallization from hexane gave 56 mg of a white solid.

Example 16

3-Butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (20)

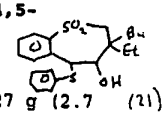


(20)

This product was isolated along with **6b** from hydrogenation of a mixture of **8a** and **8b**.

Example 17

3-Butyl-3-ethyl-4-hydroxy-5-phenylthio-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (21)



(21)

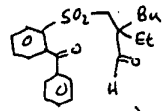
A mixture of 25 mg (0.085 mmole) of **19b**, 0.27 g (2.7 mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium carbonate, and 4 mL of DMF was stirred at room temperature under N_2 for 19 h. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed successively with 10% NaOH and brine, dried over $MgSO_4$, and concentrated in vacuo to give 0.19 g of semisolid which contain substantial amounts of diphenyl disulfide. This material was purified by HPLC (5% EtOAc-hexane) to remove diphenyl disulfide in the first fraction. The column was then eluted with 20% EtOAc-hexane to give 17 mg of a first fraction, 4 mg of a second fraction and 11 mg of a third fraction which were three different isomers of **21**, i.e. **21a**, **21b**, and **21c**, respectively, by ^1H NMR and mass spectra.

Example 18

Alternative Synthesis of 6c and 6d

A. Preparation from 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

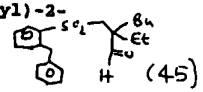
Step 1. 2-((2-Benzoylphenylsulfonyl)methyl)-2-ethylhexanal (44)



(44)

To a solution of 9.0 g (0.025 mole) of compound 2 in 100 ml of methylene chloride was added 14.6 g (0.025 mol) of 50-60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h then was stirred with 200 ml of 1 M potassium carbonate and filtered through Celite. The methylene chloride layer was washed twice with 300 ml of 1 M potassium carbonate, once with 10% sodium hydroxide and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene chloride solution was dried and concentrated in vacuo to give 9.2 g (95%)of semisolid. A portion (2.6 g) of this solid was purified by HPLC(10% ethyl acetate-hexane) to give 1.9 g of crystals, mp 135-136 °C

Step 2. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



(45)

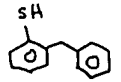
A solution of 50 g (0.13 mole) of crude 44 in 250 ml of methylene chloride was divided in two portions and charged to two Fisher-Porter bottles. To each bottle was charged 125 ml of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time but only 1 g of Pd/C was charged to the reaction mixture. The combined reaction mixture was filtered and concentrated in vacuo to give 46.8 g of 45 as brown oil.

Step 3. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)

To a solution of 27.3 g (73.4 mmole) of 45 in 300 ml of anhydrous THF cooled to 2 °C with an ice bath was added 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred for 20 min, quenched with 300 ml of 10% HCl and extracted with methylene chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give 24.7 g of yellow oil. Purification by HPLC (ethyl acetate-hexane) yielded 9.4 g of recovered 45 in the first fraction, 5.5 g (20%) of 6c in the second fraction and 6.5 g (24%) of 6d in the third fraction.

B. Preparation from 2-hydroxydiphenylmethane

Step 1. 2-mercaptodiphenylmethane (46)

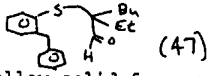


(46)

To a 500 ml flask was charged 16 g (0.33 mol) of 60% sodium hydride oil dispersion. The sodium hydride was washed twice with 50 ml of hexane. To the reaction flask was charged 100 ml of DMF. To this mixture was added a solution of 55.2 g (0.3 mol) of 2-hydroxydiphenylmethane in 200 ml of DMF in 1 h while temperature was maintained below 30 °C by an ice-water bath. After complete addition of the reagent, the mixture was stirred at room temperature for 30 min then cooled with an ice bath. To the reaction mixture was added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl chloride at once. The ice bath was removed and the reaction mixture was stirred at room temperature for 18 h before being poured into 300 ml of water. The organic was extracted into 500 ml of toluene. The toluene layer was washed successively with 10% sodium hydroxide and brine and was concentrated in vacuo to give 78.6 g of a yellow oil which was 95% pure dimethyl *O*-2-benzylphenyl thiocarbamate. This oil was heated at 280-300 °C in a kugelrohhr pot under house vacuum for 30 min. The residue was kugelrohr distilled at 1 torr (180-280 °C). The distillate (56.3 g) was crystallized from methanol to give 37.3 g (46%) of the rearranged product dimethyl

S-2-benzylphenyl thiocarbamate as a yellow solid. A mixture of 57 g (0.21 mole) of this yellow solid, 30 g of potassium hydroxide and 150 ml of methanol was stirred overnight then was concentrated in vacuo. The residue was diluted with 200 ml of water and extracted with ether. The aqueous layer was made acidic with concentrate HCl, The oily suspension was extracted into ether. The ether extract was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of 2-mercaptodiphenylmethane as a yellow solid.

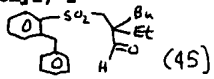
Step 2. 2-((2-Benzylphenylthio)methyl)-2-ethylhexanal (47)



(47)

A mixture of 60 g (03 mole) of yellow solid from step 1, 70 g (0.3 mole) of compound 1 from preparation 1, 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-methoxyethyl ether was held at reflux for 6 hr and concentrated in vacuo. The residue was triturated with 500 ml of water and 30 ml of concentrate HCl. The organic was extracted into 400 ml of ether. The ether layer was washed successively with brine, 10% sodium hydroxide and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2-5% ethyl acetate-hexane as eluent to give 2-((2-benzylphenylthio)methyl)-2-ethylhexanal 47 as a yellow syrup.

Step 3. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



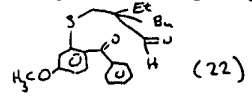
(45)

To a solution of 72.8 g (0.21 mole) of yellow syrup from step 2 in 1 liter of methylene chloride cooled to 10 °C was added 132 g of 50-60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50-60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered

through Celite. The methylene chloride solution was washed twice with 1 liter of 1 M potassium carbonate then with 1 liter of brine. The methylene chloride layer was dried over magnesium sulfate and concentrated to 76 g of 2-((2-benzylphenylsulfonyl)methyl)-2-ethylhexanal 45 as a syrup.

Step 4. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phonyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phonyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxide (6d)

Reaction of 45 with potassium t-butoxide according to the procedure in step 3 of procedure A gave pure 6c and 6d after HPLC.



(22)

Example 19

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phonyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxide (26)

Step 1. Preparation of 2-((2-benzoyl-4-methoxy phenylthio)methyl)-2-ethylhexanal (22)

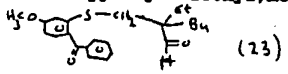
2-Hydroxy-4-methoxybenzophenone was converted to the dimethyl *O*-2-benzoyphenyl thiocarbamate by methods previously described in example 18. The product can be isolated by recrystallization from ethanol. Using this improved isolation procedure no chromatography was needed. The thermal rearrangement was performed by reacting the thiocarbamate(5 g) in diphenyl ether at 260 °C as previously described. The improved isolation procedure which avoided a chromatography step was described below.

The crude pyrolysis product was then heated at 65 °C in 100 ml of methanol and 100 ml of THF in the presence of 3.5 g of KOH for 4 h. After removing THF and methanol

by rotary evaporation the solution was extracted with 5 % NaOH and ether. The base layer was acidified and extracted with ether to obtain a 2.9 g of crude thiophenol product. The product was further purified by titrating the desired mercaptan into base with limited KOH. After acidification and extraction with ether pure 2-mercapto-4-methoxybenzophenone (2.3 g) was isolated.

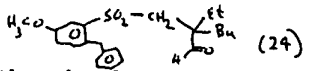
2-mercapto-4-methoxybenzophenone can readily be converted to the 2-((2-benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (**22**) by reaction with 2-ethyl-2-(mesyloxymethyl)hexanal (**1**) as previously described.

Step 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (23)



(23)

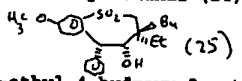
Substrate **22** was readily oxidized to **2-((2-benzoyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (23)** as described in example 18.



(24)

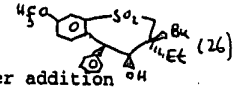
Step 3. 2-((2-benzyl-5-mothoxyphenylsulfonyl)methyl)-2-ethylhexanal (24)

Sulfone **23** was then reduced to **2-((2-benzyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (24)** as described in example 18.



(25)

Step 4. (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiopine-1,1-dioxide (25) and (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26)

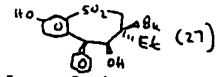


(26)

A 3-neck flask equipped with a powder addition funnel,thermocouple and nitrogen bubbler was charged with 19.8 g (0.05 mole) of sulfone **24** in 100 ml dry THF. The reaction was cooled to -1.6 °C internal

temperature by means of ice/salt bath. Slowly add 5.61 g (0.05 mole) of potassium t-butoxide by means of the powder addition funnel. The resulting light yellow solution was maintained at -1.6 °C. After 30 min reaction 400 ml of cold ether was added and this solution was extracted with cold 10 % HCl. The acid layer was extracted with 300 ml of methylene chloride. The organic layers were combined and dried over magnesium sulfate and after filtration stripped to dryness to obtain 19.9 g of product. ^{1}H nmr and glpc indicated a 96% conversion to a 50/50 mixture of **25** and **26**. The only other observable compound was 4% starting sulfone **24**.

The product was then dissolved in 250 ml of 90/10 hexane/ethyl acetate by warming to 50 °C. The solution was allowed to cool to room temperature and in this way pure **26** can be isolated. The crystallization can be enhanced by addition of a seed crystal of **26**. After 2 crystallizations the mother liquor which was now 85.4% **25** and has a dry weight of 8.7 g. This material was dissolved in 100 ml of 90/10 hexane/ethyl acetate and 10 ml of pure ethyl acetate at 40 C. Pure **25** can be isolated by seeding this solution with a seed crystal of **25** after storing it overnight at 0 C.



(27)

Example 20

(3a,4a,5a) 3-Butyl-3-ethyl-4,8-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (27)

In a 25 ml round bottomed flask, 1 g of **26**(2.5 mmoles) and 10 ml methylene chloride were cooled to - 78 °C with stirring. Next 0.7 ml of boron tribromide(7.5 mmole) was added via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 6 h. The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water.The organic layer was dried over magnesium

sulfate. The product (0.88g) **27** was characterized by NMR and mass spectra.

Example 21

General Alkylation of phenol 27

A 25 ml flask was charged with 0.15 g of **27**(0.38 mmole), 5 ml anhydrous DMF, 54 mg of potassium carbonate(0.38 mmole) and 140 mg ethyl iodide (0.9 mmole). The reaction was stirred at room temperature overnight.The reaction was diluted with 50 ml ethyl ether and washed with water (25 ml) then 5% NaOH (20 ml) and then sat. NaCl. After stripping off the solvent the ethoxylated product **28** was obtained in high yield. The product was characterized by NMR and mass spectra. This same procedure was used to prepare products listed in table 1 from the corresponding iodides or bromides. For higher boiling alkyl iodides and bromides only one equivalent of the alkyl halide was used.

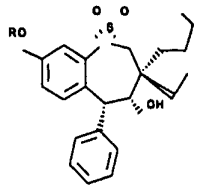


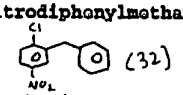
Table 1

Compound No.	R
27	H
26	Me
28	Et
29	hexyl
30	Ac
31	(CH2)6-N-pthalimide

Example 22

(3a,4a,5a) 3-Butyl-3-ethyl-6-hydroxy-7-hydroxyamino-5-phonyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxido (37) and (3a,4b,5b) 3-Butyl-3-ethyl-6-hydroxy-7-hydroxyamino-5-phonyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxido (38)

Step 1. Preparation of 2-chloro-5-nitrodiphonylmethane (32)

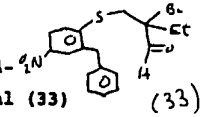


(32)

Procedure adapted from reference :Synthesis -Stuttgart 9 770-772 (1986) Olah G. Et al

Under nitrogen, a 3 neck flask was charged with 45 g (0.172 mole) of 2-chloro-5-nitrobenzophenone in 345 ml methylene chloride and the solution was cooled to ice/water temperature. By means of an additional funnel, 150 g(0.172 mole) of trifluoromethane sulfonic acid in 345 ml methylene chloride was added slowly. Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride was added dropwise to the chilled solution. Both addition steps(trifluoromethane sulfonic acid and triethylsilane)were repeated. After the additions were completed the reaction was allowed to slowly warm up to room temperature and stirred for 12 h under nitrogen. The reaction mixture was then poured into a chilled stirred solution of 1600 ml of saturated sodium bicarbonate. Gas evolution occurred. Poured into a 4 liter separatory funnel and separated layers. The methylene chloride layer was isolated and

combined with two 500 ml methylene chloride extractions of the aqueous layer. The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give 39 g product. Structure **32** was confirmed by mass spectra and proton and carbon NMR.

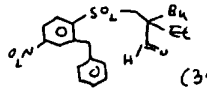


Step 2. Preparation of 2-((2-benzyl-4-nitrophonylthio)mothyl)-2-ethylhexanal (33) (33)

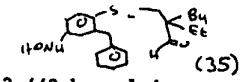
The 2-chloro-5-nitrodiphenylmethane product **32** (40 g, 0.156 mole) from above was placed in a 2 liter 2 neck flask with water condenser. Next 150 ml DMSO and 7.18 g (0.156 mole) of lithium sulfide was added and the solution was stirred at 75 °C for 12 h. The reaction was cooled to room temperature and then 51.7 g of mesylate IV was added in 90 ml DMSO. The reaction mixture was heated to 80 °C under nitrogen. After 12 h monitored by TLC and added more mysylate if necessary. Continued the reaction until the reaction was completed. Next the reaction mixture was slowly poured into a 1900 ml of 5% acetic aqueous solution with stirring, extracted with 4 X 700 ml of ether, and dried over MgSO4. After removal of ether, 82.7 g of product was isolated. The material can be further purified by silica gel chromatography using 95% hexane and 5 % ethyl acetate. If pure mysylate was used in this step there was no need for further purification. The product **33** was characterized by mass spectra and NMR.

Step 3. Oxidation of the nitro product 33 to the sulfone 2-((2-benzyl-4-nitrophenylsulfonyl)methyl)-2-ethylhexanal (34)

The procedure used to oxidize the sulfide **33** to the sulfone **34** has been previously described.



(34)

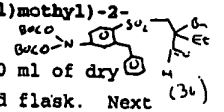


(35)

Step 4. Reduction of 34 to 2-((2-benzyl-4-hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (35)

A 15 g sample of **34** was dissolved in 230 ml of ethanol and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt.% Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate **34** was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product **35** was isolated by filtering off the Pd/C and then stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

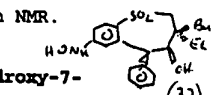
Step 5. Preparation of the 2-((2-benzyl-4-*N,O*-di-(t-butoxy-carbonyl)hydroxyaminophonylsulfonyl)mothyl)-2-ethylhexanal (36).



(36)

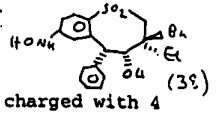
A 13.35 g sample of **35** (0.0344 mole) in 40 ml of dry THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of di-t-butyl dicarbonate in 7 ml THF. Heated at 60 °C overnight. Striped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.

The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product **36** was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.



(37)

Step 6. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiopine-1,1-dioxide (37) and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiopino-1,1-dioxide (38)

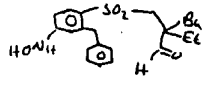


(38)

A 250ml 3-neck round bottomed flask was charged with 4 g of **36** (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78 °C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide(20.4 mmoles) with

stirring and maintaining a -78 °C reaction temperature. After 1 h at -78 °C the addition of base was completed and the temperature was brought to -10 °C by means of a ice/salt bath. After 3 h at -10 °C, only trace **36** remained by TLC. Next add 35 ml of deionized water to the reaction mixture at -10 °C and stirred for 5 min. Striped off most of the THF and added to separatory funnel and extracted with ether until all of the organic was removed from the water phase. The combined ether phases were washed with saturated NaCl and then dried over sodium sulfate. The only products by TLC and NMR were the two BOC protected isomers of **37** and **38**. The isomers were separated by silica gel chromatography using 85% hexane and 15 % ethyl acetate; **BOC-37** (0.71 g) and **BOC- 38** (0.78 g).

Next the BOC protecting group was removed by reacting 0.87 g of **BOC-38** (1.78 mmoles) with 8.7 ml of 4 M HCl (34.8 mmoles)in dioxane for 30 min. Next added 4.74 g of sodium acetate (34.8 mmoles) to the reaction mixture and 16.5 ml ether and stirred until clear. After transferring to a separatory funnel extracted with ether and water and then dried the ether layer with sodium sulfate. After removing the ether, 0.665 g of **38** was isolated. Isomer **37** could be obtained in a similar procedure.



(39)

Example 23

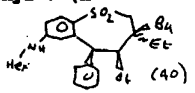
(3a,4a,5a) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (40) and (3a,4b,5b) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (41)

Step 1. 2-((2-Benzyl-4-(n-hexylamino)phenylsulfonyl)methyl)-2-ethylhexanal (39)

In a Fischer porter bottle weighed out 0.5 g of **36** (1.2 mmoles) and dissolved in 3.8 ml of ethanol under

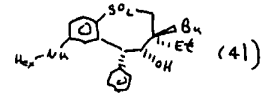
nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexanal. Seal and pressure to 50 psi of hydrogen gas. Stirred for 48 h. After filtering off the catalyst and removing the solvent by rotary evaporation **39** was isolated by column chromatography (0.16 g) using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. The product was characterized by NMR and mass spectra.

Step 2. (3a,4a,5a) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (40) and (3a,4b,5b) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (41)



(40)

A 2-neck, 25 ml round bottomed flask with stir bar was charged with 0.158 g **39** (0.335 mmole) and 5 ml anhydrous THF under nitrogen. Cool to -10 °C by means of a salt/water bath. Slowly add 0.113 g of potassium tert butoxide (0.335 mmole). After 15 min at -10 °C all of the starting material was consumed by TLC and only the two isomers **40** and **41** were observed. Next added 5 ml of chilled 10% HCl and stirred at -10 °C for 5 min. Transferred to a separatory funnel and extract with ether. Dried over sodium sulfate. Proton NMR of the dried product (0.143 g) indicated only the presence of the two isomers **40** and **41**. The two isomers were separated by silica gel chromatography using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. **40** (53.2 mg); **41**(58.9 mg).



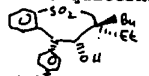
(41)

Example 24

Quaternization of amine substrates 40 and 41

Amine products such as **40** and **41** can be readily alkylated to quaternary salts by reaction with alkyl halides. For example **40** in DMF with 5 equivalents of

methyl iodide in the presence of 2,6 dimethyl lutidine produces the dimethylhexylamino quaternary salt.

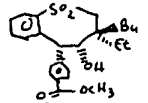


(42)

Example 25

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (42)

In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of **6d**, 0.67 g of mercuric triflate were dissolved in 20 ml of dry methylene chloride with stirring. Next 0.34 g of Iodine was added and the solution was stirred at room temperature for 30 h. The reaction was then diluted with 50 ml methylene chloride and washed with 10 ml of 1 M sodium thiosulfate; 10 ml of saturated KI ; and dried over sodium sulfate. See Tetrahedron, Vol.50, No. 17, pp 5139-5146 (1994) Bachki, F. Et al.Mass spectrum indicated a mixture of **6d** , mono iodide **42** and a diiodide adduct. The mixture was separated by column chromatography and **42** was characterized bt NMR and mass spectra.



(43)

Example 26

(3a,4b,5b) 3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (43)

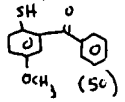
A 0.1 g sample of **42** (0.212 mmole), 2.5 ml dry methanol, 38 µl triethylamine (0.275 mmole) , 0.3 ml toluene and 37 mg of palladium chloride (0.21 mmole) was charged to a glass lined mini reactor at 300 psi carbon monoxide. The reaction was heated at 100 °C overnight. The catalyst was filtered and a high yield of product was isolated.
The product was characterized by NMR and mass spectra.

Note the ester functionalized product **43** can be converted to the free acid by hydrolysis.

Example 27

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)

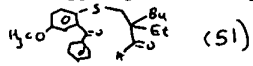
Step 1. 2-Mercapto-5-methoxybenzophenone (50)



(50)

Reaction of 66.2 g of 4-methoxythiophenol with 360 ml of 2.5 N n-butyllithium, 105 g of tetramethylethylenediamine and 66.7 g of benzonitrile in 600 ml cyclohexane according to the procedure in WO 93/16055 gave 73.2 g of brown oil which was kugelrohr distilled to remove 4-methoxythiophenol and gave 43.86 g of crude **50** in the pot residue.

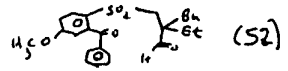
Step 2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (51)



(51)

Reaction of 10 g (0.04 mole) of crude **50** with 4.8 g (0.02 mole)of mesylate **1** and 3.2 ml (0.23 mole) of triethylamine in 50 ml of diglyme according to the procedure for the preparation of **2** gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-hexane) to give 1.7 g (22%) of **51**.

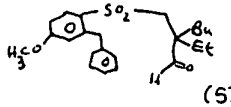
Step 3. 2-((2-Benzoyl-4-methoxyphenylsulfonyl)methyl)-2-ethyl-hexanal (52)



(52)

A solution of 1.2 g (3.1 mmoles) of **51** in 25 ml of methylene chloride was reacted with 2.0 g (6.2 mmoles) of 50-60% MCPBA according to the procedure of step 2 of procedure A in example 18 gave 1.16 g (90%) of **52** as a yellow oil.

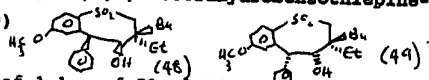
Step 4. 2-((2-Benzyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (53)



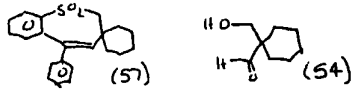
(53)

Hydrogenation of 1.1 g of **52** according to the procedure of step 3 of procedure A of example 18 gave **53** as a yellow oil (1.1 g).

Step 5. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)


(48) (49)

A solution of 1.1 g of **53**, 0.36 g of potassium t-butoxide and 25 ml of anhydrous THF was held at reflux for 2 h and worked up as in step 4 of procedure A of example 18 to give 1.07 g of a crude product which was purified by HPLC to give 40 mg (4%) of **48** as crystals, mp 153-154 °C and 90 mg (8%) of **49** as solid, mp 136-140 °C.


(57) (54)

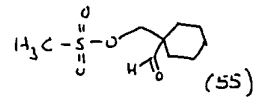
Example 28

5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)

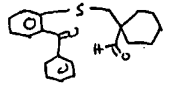
Step 1. 1-(Hydroxymethyl)-cyclohexanocarboxaldehyde (54)

To a cold (0 °C) mixture of 100 g (0.891 mole) of cyclohexanecarboxaldehyde, 76.5 g of 37% of formaldehyde in 225 ml of methanol was added dropwise 90 ml of 1 N Sodium hydroxide in 1 h. The reaction mixture was stirred at room temperature over 48 then was evaporated to remove methanol. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 75 g (59.7%) of thick oil. Proton NMR and mass spectra were consistent with the product.

Step 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde (55)


(55)

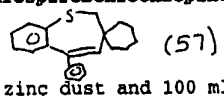
To a cold (0 °C) mixture of alcohol **54** (75 g, 0.54 mole) and 65.29 g (0.57 mole) of methanesulfonyl chloride in 80 ml of methylene chloride was added a solution of pyridine (47.96 g, 0.57 mole) in 40 ml of methylene chloride. The reaction mixture was stirred at room temperature for 18 h then quenched with water, acidified with conc. HCl and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 91.63 g (77.8%) of thick oil. Proton NMR and mass spectra were consistent with the product.


(56)

Step 3. 1-((2-Benzoylphenylthio)methyl)cyclohexanocarboxaldehyde (56)

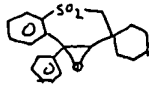
A mixture of 69 g (0.303 mole) of 2-mercaptobenzophenone, 82 g (0.303 mole) of mesylate **55**, 32 g of triethylamine, and 150 ml of diglyme was stirred and held at reflux for 24 h. The mixture was cooled, poured into dil. HCl and extracted with methylene chloride. The organic layer was washed with 10% NaOH, water, brine, and dried over sodium sulfate and concentrated under vacuum to remove excess diglyme. This was purified by silica gel flush column (5% EtOAc: Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton NMR and mass spectra were consistent with the product.

Step 4. 5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)


(57)

To a mixture of 6.19 g of zinc dust and 100 ml of dry DME was added $TiCl_4$ (16.8 g, 0.108 mole) . The reaction mixture was heated to reflux for 2 h. A solution of compound **56** (8.3 g, 0.023 mole) in 50 ml of DME was added dropwise to the reaction mixture in 1 h and the mixture was held at reflux for 18 h. The mixture was

cooled, poured into water and extracted with ether. The organic layer was washed with water, brine, and dried over sodium sulfate, filtered through celite and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white solid, mp 90-91 °C. Proton and carbon NMR and mass spectra were consistent with the product.

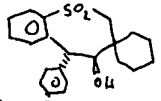


(58)

Example 29

8b-Phenyl-1a,2,3,8b-tetrahydrospiro(benzothiopino[4,5-b]oxireno-2,1'-cyclohexane)-4,4-dioxide (58)

To a solution of 57 (4.6 g, 15 mmole) in 50 ml chloroform under nitrogen was added 55% MCPBA (16.5 g, 52.6 mmole) portionwise with spatula. The reaction was held at reflux for 18 h and washed with 10% NaOH(3X), water, brine, and dried over sodium sulfate and concentrated under vacuum to give 5 g of crude product. This was recrystallized from Hexane/EtOAc to give 4.31 g (81%) of yellow solid, mp 154-155 °C. Proton and carbon NMR and mass spectra were consistent with the product.

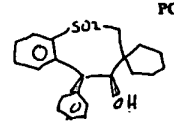


(59)

Example 30

trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiopino-3,1'-cyclohexane)-1,1-dioxide (59)

A mixture of 0.5 g (1.4 mmoles) of 58 , 20 ml of ethanol,10 ml of methylene chloride and 0.4 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to dryness. The residue was purified by HPLC (10% EtOAc-Hexane, 25% EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was a trans isomer. The second fraction gave 200 mg of solid which was impure cis isomer.

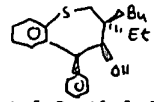


(60)

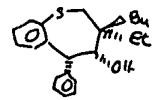
Example 31

cis-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiopino-3,1'-cyclohexane)-1,1-dioxide (60)

To a solution of 0.2 g (0.56 mmole) of 59 in 20 ml of CH_2Cl_2, was added 8 g of 50% NaOH and one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst. The reaction mixture was stirred for 10 h at room temperature. Twenty g of ice was added to the mixture and the mixture was extracted with CH_2Cl_2 (3x10 ml) washed with water, brine and dried over $MgSO_4$ and concentrated in vacuo to recover 0.15 g of crude product. This was recrystallized from Hexane/EtOAc to give 125 mg of white crystal, mp 209-210 °C . Proton and carbon NMR and mass spectra were consistent with the product.



(61)



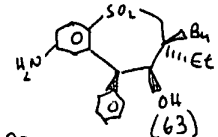
(62)

Example 32

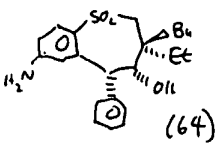
(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiopine (61), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiopino (62)

To a solution of 0.5 g (1.47 mmole) of compound 47 in 5 ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred at room temperature for 18 h and quenched with 10 ml of 10% HCl. The organic was extracted into methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by HPLC (2% EtOAc-hexane) to give 47 mg of 61 in the second fraction and 38 mg of 62 in the third fraction. Proton NMR and mass spectra were consistent with the assigned structures.

Example 33



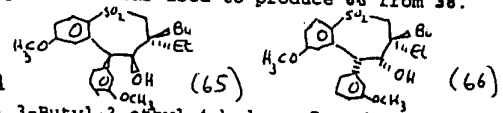
(63)



(64)

(3a,4a,5a) 3-Butyl-3ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (63) and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide(64)

An autoclave was charged with 200 mg of 37 in 40 cc ethanol and .02 g 10 % Pd/C. After purging with nitrogen the clave was charged with 100 psi hydrogen and heated to 55 C. The reaction was monitored by TLC and mass spec and allowed to proceed until all of 37 was consumed. After the reaction was complete the catalyst was filtered and the solvent was removed in vacuo and the only observable product was amine 63. This same procedure was used to produce 64 from 38.



(65) (66)

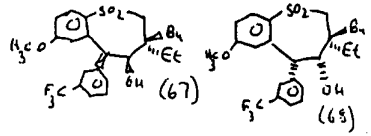
Example 34

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (65), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (66).

Alkylation of e-methoxyphenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-methoxybenzyl)phenol in 35% yield. This material was converted to compound 65, mp 138.5-141.5 °C, and compound 66, mp 115.5-117.5 °C, by the procedure similar to that in Example 18 method B.

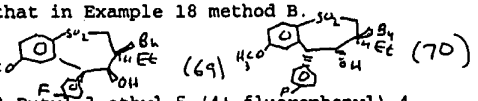
Example 35

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (67), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (68).



(67) (68)

Alkylation of 4-methoxyphenol with 3-(trifluoromethyl)benzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-(trifluoromethyl)benzyl)phenol. This material was converted to compound 67, mp 226.5-228 °C, and compound 68, mp 188-190°C, byu the procedure similar to that in Example 18 method B.

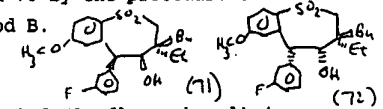


(69) (70)

Example 36

(3a,4a,5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (69), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (70).

Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(4'-fluorobenzyl)phenol. This material was converted to compound 69 and compound 70 by the procedure similar to that in Example 18 method B.



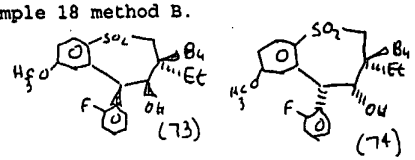
(71) (72)

Example 37

(3a,4a,5a) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (71), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (72).

Alkylation of 4-methoxyphenol with 3-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-fluorobenzyl)phenol. This material was converted to compound 71 and compound 72 by the procedure similar to that in Example 18 method B.

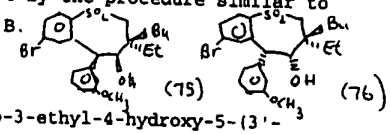
Example 38



(73) (74)

(3a,4a,5a) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).

Alkylation of 4-methoxyphenol with 2-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

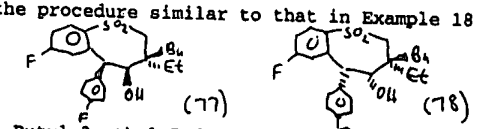


(75) (76)

Example 39

(3a,4a,5a) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (75), and (3a,4b,5b) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).

Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.



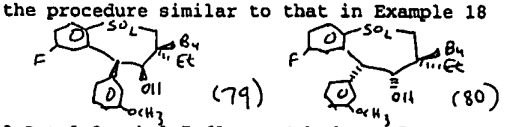
(77) (78)

Example 40

(3a,4a,5a) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (77), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (78).

Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J.

Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230 °C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

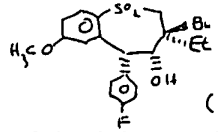


(79) (80)

Example 41

(3a,4a,5a) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-40hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (80).

Alkylation of 4-fluorophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-methoxybenzyl)phenol. This material was converted to compound 79, as a solid and compound 80, mp 153-155 °C, by the procedure similar to that in Example 18 method B.

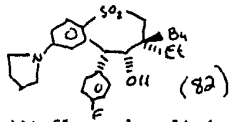


(81)

Example 42

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (81).

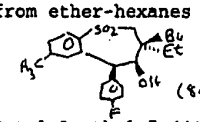
A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was dilute with ether and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20% ethyl acetate in hexanes). The first fraction was impure (3a,4a,5a) 3-butyl-3-ethyl-4-hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide. The second fraction was compound 81, mp 185-186.5 °C.

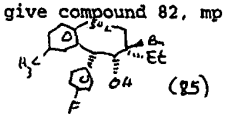


Example 43

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-pyrrolidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (82).

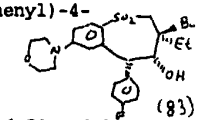
A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml of pyrrolidine was held at reflux for 1 h. The reaction mixture was diluted with ether and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was crystallized from ether-hexanes to give compound 82, mp 174.5-177 °C.





Example 44

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-morpholinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (83).



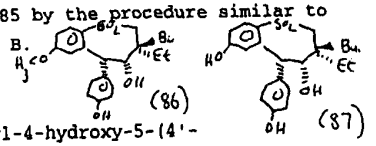
A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g (56 mmol) of morpholine was held at reflux for 2 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was recrystallized from ether-hexanes to give compound 83, mp 176.5-187.5 °C.

Example 45

(3a,4a,5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (84), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (85).

Alkylation of 4-methylphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methyl-2-(4'-fluorobenzyl)phenol). This material was converted to

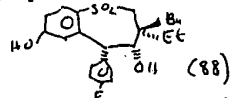
compound 84 and compound 85 by the procedure similar to that in Example 18,method B.



Example 46

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4'-hydroxyphenyl)-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (86), and (3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (87).

To a solution of 0.52 (1.2 mmol) of compound 66 in 20 ml of methylene chloride was added 1.7 g (6.78 mmol) of born tribromide. The reaction mixture was cooled to -78 °C and was stirred for 4 min. An additional 0.3 ml of boron tribromide was added to the reaction mixture and the reaction mixture was stirred at -78 °C for 1 h and quenced with 2 N HCl. The organic was extracted into ether. The ether layer was washed with brine, dried over M_gSO_4, and concentrated in vacuo. The residue (0.48 g) was purified by HPLC (30% ethyl acetate in hexanes). The first fraction was 0.11 g of compound 86 as a white solid, mp 171.5-173 °C. The second fraction was crystallized from chloroform to give 0.04 g of compound 87 as a white solid, mp 264 °C (dec).

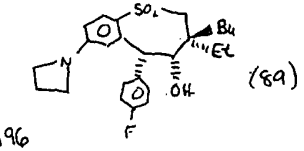


Example 47

(3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (88).

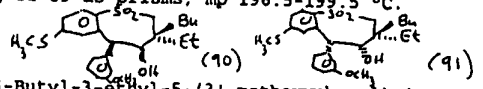
Reaction of compound 70 with excess boron tribromide at room temperature and worked up as in Example 46 gave compound 88 after an HPLC purification.

Example 48



(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-azetidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (89).

A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 g (35 mmol) of aztidine was held at reflux for 3 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over MgSO4. The ether solution was concentrated on a steam bath. The separated crystals were filtered to give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.



Example 49

(3a,4a,5a) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (90). (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (91).

A mixture of 0.4 g (0.95 mmol) of compound 79, 0.08 g (1.14 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at 60 °C for 2 h. An additional 1.4 mmol of sodium methanethiolate was added to the reaction mixture and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was triturated with 100 ml of water and extracted methylene chloride. The methylene chloride water mixture was filtered through Celite and the methylene chloride layer was dried over M_gSO_4 and concentrated in vacuo. The first fraction (0.1 g) was compound 90, mp 117-121 °C. The second fraction (0.16 g) was compound 91, mp 68-76 °C.

A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_4$ and 80 mL of anhydrous ethylene glycol dimethyl ether (DME) was held at reflux for 2 h. The reaction mixture was cooled to 5 °C. To the reaction mixture was added dropwise a solution of 3.54 g (0.01 mole) of **2** in 30 mL of DME in 40 min. The reaction mixture was stirred at room temperature for 16 h and then was held at reflux for 2 h and cooled before being poured into brine. The organic was extract into methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (hexane) to give 1.7 g (43%) of **3** as an oil in the first fraction. The second fraction was discarded and the third fraction was further purified by HPLC (hexane) to give 0.07 g (2%) of **4a** in the earlier fraction and 0.1 g (3%) of **4b** in the later fraction.

Example 2

cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5_H_)4-one-1,1-dioxide (5a) and _trans_-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5_H_)4-one-1,1-dioxide (5b)

To a solution of 1.2 g (3.5 mmole) of 50-60% MCPBA in 20 mL of methylene chloride was added 0.59 g (1.75 mmole) of a mixture of **4a** and **4b** in 10 mL of methylene chloride. The reaction mixture was stirred for 20 h. An additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added and the reaction mixture was stirred for an additional 3 h then was triturated with 50 mL of 10% NaOH. The insoluble solid was filtered. The methylene chloride layer of the filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual syrup was purified by HPLC (5% EtOAc-hexane) to give 0.2 g (30%)of **5a** as an oil in the first fraction and 0.17 g (26%) of **5b** as an oil in the second fraction.

Example 3

(3a,4a,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxide (6a), (3a,4b,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxide (6b), (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxide (6c), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepino-1,1-dioxide (6d)

A. Reduction of 5a and 5b with Sodium Borohydride

To a solution of 0.22 g (0.59 mmole) of **5b** in 10 mL of ethanol was added 0.24 g (6.4 mmole) of sodium borohydride. The reaction mixture was stirred at room temperature for 18 h and concentrated in vacuo to remove ethanol. The residue was triturated with water and extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo to give 0.2 g of syrup. In a separate experiment, 0.45 g of **5a** was treated with 0.44 g of sodium borohydride in 10 mL of ethanol and was worked up as described above to give 0.5 g of syrup which was identical to the 0.2 g of syrup obtained above. These two materials were combined and purified by HPLC using 10% EtOAc-hexane as eluant. The first fraction was 0.18 g (27%) of **6a** as a syrup. The second fraction was 0.2 g (30%) of **6b** also as a syrup. The column was then eluted with 20% EtOAc-hexane to give 0.077 g (11%) of **6c** in the third fraction as a solid. Recrystallization from hexane gave a solid, mp 179-181 °C. Finally, the column was eluted with 30% EtOAc-hexane to give 0.08 g (12%) of **6d** in the fourth fraction as a solid. Recrystallization from hexane gave a solid, mp 160-161 °C.

B. Conversion of 6a to 6c and 6d with NaOH and PTC

To a solution of 0.29 g (0.78 mmole) of **6a** in 10 mL CH_2Cl_2, was added 9 g of 40% NaOH. The reaction mixture was stirred for 0.5 h at room temperature and was added one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst (PTC). The mixture was stirred for 0.5 h at room temperature before being treated with 25 mL of ice-crystals then was extracted with CH_2Cl_2 (3x10 ml), dried over $MgSO_4$ and concentrated in vacuo to recover 0.17 g of a colorless film. The components of this mixture were separated using an HPLC and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2-(2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the first fraction, 30.9 mg (11%) of **6c** in the second fraction and 90.0 mg (31%) of **6d** in the third fraction.

Oxidation of 6a to 5b

To a solution of 0.20 g (0.52 mmole) of **6a** in 5 mL of CH_2Cl_2 was added 0.23 g (1.0 mmole) of pyridinium chlorochromate. The reaction mixture was stirred for 2 h then was treated with additional 0.23 g of pyridinium chlorochromate and stirred overnight. The dark reaction mixture was poured into a ceramic filterfrit containing silica gel and was eluted with CH_2Cl_2. The filtrate was concentrated in vacuo to recover 167 mg (87%) of **5b** as a colorless oil.

Example 4

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-dioxide (7)

To a solution of 5.13 g (15.9 mmole) of **3** in 50 mL of CH_2Cl_2 was added 10 g (31.9 mmole) of 50-60% MCPBA (m-chloroperoxybenzoic acid) portionwise causing a mild reflux and formation of a white solid. The reaction mixture was allowed to stir overnight under N_2 and was triturated with 25 mL of water followed by 50 mL of 10% NaOH solution. The organic was extracted into CH_2Cl_2 (4x20 mL). The CH_2Cl_2 extract was dried over $MgSO_4$ and evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

Example 5

(1aa,2b,8ba) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (8a) (1aa,2a,8ba) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino [4,5-*b*]oxirene-4,4-dioxide (8b)

To 1.3 g (4.03 mole) of **3** in 25 mL of $CHCl_3$ was added portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a mild exotherm. The reaction mixture was stirred under N_2 overnight and was then held at reflux for 3 h. The insoluble white slurry was filtered. The filtrate was extracted with 10% potassium carbonate (3x50 mL), once with brine, dried over $MgSO_4$, and concentrated in vacuo to give 1.37 g of a light yellow oil. Purification by HPLC gave 0.65 g of crystalline product. This product is a mixture of two isomers. Trituration of this crystalline product in hexane recovered 141.7 mg (10%) of a white crystalline product. This isomer was characterized by NMR and mass spectra to be the (1aa,2b,8ba) isomer **8a**. The hexane filtrate was concentrated in vacuo to give 206 mg of white film which is a mixture of 30% **8a** and 70% **8b** by ^1H NMR.

Example 6

cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (9a), trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (9b), and 3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidine-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (10)

A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of **8a** and **8b** was dissolved in 15 ml MeOH in a 3 oz. Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C catalyst. This mixture was hydrogenated at 70 psi H_2 for 5 h and filtered. The filtrate was evaporated to dryness in vacuo to recover 0.117 g of a colorless oil. This material was purified by HPLC eluting with EtOAc-hexane. The first fraction was 4.2 mg (3%) of **9b**. The second fraction, 5.0 mg (4%), was a 50/50 mixture of **9a** and **9b**. The third fraction was 8.8 mg (6%) of **6a** . The fourth fraction was 25.5 mg (18%) of **6b**. The fifth fraction was 9.6 mg (7%) of a mixture of **6b** and a product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide based on mass spectrum. The sixth fraction was 7.5 mg (5%) of a mixture of **6d** and one of the isomers of **10**, **10a**.

Example 7

In another experiment, a product (3.7 g) from epoxidation of **3** with excess MCPBA in refluxing $CHCl_3$ under air was hydrogenated in 100 mL of methanol using 1 g of 10% Pd/C catalyst and 70 psi hydrogen. The product was purified by HPLC to give 0.9 g (25%) of **9b**, 0.45 g (13%) of **9a**, 0.27 g (7%) of **6a**, 0.51 g (14%) of **6b**, 0.02 g (1%) of **6c**, 0.06 g (2%) of one isomer of **10**, **10a** and 0.03 g (1%) of another isomer of **10**, **10b**.

Example 8

2-((2-Benzoylphenylthio)methyl)butyraldehyde (11)

To an ice bath cooled solution of 9.76 g (0.116 mole) of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g (0.116 mole) of 2-mercaptobenzophenone in 40 mL of THF followed by 13 g (0.128 mole) of triethylamine. The reaction mixture was stirred at room temperature for 3 days , diluted with ether, and was washed successively with dilute HCl, brine, and 1 M potassium carbonate. The ether layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc-hexane) to give 22 g (64%) of **11** in the second fraction. An attempt to further purifiy this material by kugelrohr distillation at 0.5 torr (160-190 °C) gave a fraction (12.2 g) which contained starting material indicating a reversed reaction during distillation. This material was dissolved in ether (100 mL) and was washed with 50 mL of 1 M potassium carbonate three times to give 6.0 g of a syrup which was purified by HPLC (10% EtOAc-hexane) to give 5.6 g of pure **11**.

Example 9

3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine (12)

To a mixture of 2.61 g (0.04 mole) of zinc dust and 60 mL of DME was added 7.5 g (0.048 mole) of $TiCl_3$. The reaction mixture was held at reflux for 2 h. A solution of 2.98 g (0.01 mole) of **11** was added dropwise in 1 h. The reaction mixture was held at reflux for 18 h, cooled and poured into water. The organic was extracted into ether. The ether layer was washed with brine and filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated. The residual oil (2.5 g) was purified by HPLC to give 2.06 g (77%) of **12** as an oil in the second fraction.

Example 10

(1aa,2a,8ba) 2-Ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino-[4,5-b]oxireno-4,4-dioxide (13)

To a solution of 1.5 g (5.64 mmole) of **12** in 25 ml of $CHCl_3$ was added 6.8 g (19.4 mmole) of 50-60% MCPB portionwise causing an exothem and formation of a white solid. The mixture was stirred at room temperature overnight diluted with 100 ml methylene chloride and washed successively with 10% K_2CO_3 (4x50 ml), water (twice with 25 ml) and brine. The organic layer was then dried over $MgSO_4$ and evaporated to dryness to recover 1.47 g of an off white solid. ^1H NMR indicated that only one isomer is present. This solid was slurried in 200 ml of warm Et_2O and filtered to give 0.82 g (46%) of **13** as a white solid, mp 185-186.5 °C.

Example 11

(3a,4b,5a)- 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-totrahydro-benzothiepine-1,1-dioxide (14a), (3a,4b,5b) 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (14b), and cis-3-Ethyl-5-phenyl-2,3,4,5-totrahydro-benzothiepino-1,1-dioxide (15)

A mixture of 0.5 g (1.6 mole) of **13**, 50 ml of acetic acid and 0.5 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 4 h. The crude reaction slurry was filtered and the filtrate was stirred with 150 ml of a saturated $NaHCO_3$ solution followed by 89 g of $NaHCO_3$ powder portionwise to neutralize the rest of acetic acid. The mixture was extracted with methylene chloride (4x25 ml), then the organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 0.44 g (87%) of a voluminous white solid which was purified by HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of **15** in the first fraction, 272 mg (54%) of **14a** as a solid, mp 142-143.5 °C, in the second fraction, and 35 mg (7%) of impure **14b** in the third fraction.

Example 12

2-Ethyl-2-((2-Hydroxymethylphenyl)thiomethyl)hexenal (16)

A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl alcohol, 6.4 g (0.032 mole) of 1, 3.6 g (0.036 mole) of triethylamine and 25 mL of 2-methoxyethyl ether was held at reflux for 7 h. Additional 1.1 g of mercaptobenzyl alcohol and 0.72 g of triethylamine was added to the reaction mixture and the mixture was held at reflux for additional 16 h. The reaction mixture was cooled and poured into 6N HCl and extracted with methylene chloride. The methylene chloride extract was washed twice with 10% NaOH, dried over $MgSO_4$ and concentrated in vacuo to give 9.6 g of residue. Purification by HPLC (20% EtOAc-hexane) gave 3.7 g (41%)of **16** as an oil.

Example 13

2-Ethyl-2-((2-formylphenyl)thiomethyl)hexenal (17)

A mixture of 3.7 g of **16**, 5.6 g (0.026 mole) of pyridinium chlorochromate, 2 g of Celite and 30 mL of methylene chloride was stirred for 18 h and filtered through a bed of silica gel. The silica gel was eluted with methylene chloride. The combined methylene chloride eluant was purified by HPLC (20% ETOAc-hexane) to give 2.4 g (66%) of an oil.

Example 14

3-Butyl-3-ethyl-2,3-dihydrobenzothiepine (18)

A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_4$, and 50 mL of DME was held at reflux for 2 h and cooled to room temperature. To this mixture was added 2.4 g (8.6 mmole) of **17** in 20 mL of DME in 10 min. The reaction mixture was stirred at room

temperature for 2 h and held at reflux for 1 h then was let standing at room temperature over weekend. The reaction mixture was poured into dilute HCl and was stirred with methylene chloride. The methylene chloride-water mixture was filtered through Celite. The methylene chloride layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 3.0 g of a residue. Purification by HPLC gave 0.41 g (20%) of **18** as an oil in the early fraction.

Example 15

(1aa,2a,8ba) 2-Butyl-2-ethyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (19a) and (1aa,2b,8ba) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (19b)

To a solution of 0.4 g of 0.4 g (1.6 mmole) of **18** in 30 mL of methylene chloride was added 2.2 g (3.2 mmole) of 50-60% MCPBA. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was dissolved in 30 mL of $CHCl_3$ and was held at reflux for 18 h under N_2. The reaction mixture was stirred with 100 mL of 10% NaOH and 5 g of sodium sulfite. The methylene chloride layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (20% EtOAc-hexane) to give a third fraction which was further purified by HPLC (10% EtOAc-hexane) to give 0.12 g of syrup in the first fraction. Recrystallization from hexane gave 0.08 g (17%) of **19a**, mp 89.5-105.5 °C. The mother liquor from the first fraction was combined with the second fraction and was further purified by HPLC to give additional **19a** in the first fraction and 60 mg of **19b** in the second fraction. Crystallization from hexane gave 56 mg of a white solid.

Example 16

3-Butyl-3-ethyl-6,5-dihydroxy-5-phenyl-2,3,6,5-tetrahydro-benzothiepine-1,1-dioxide (20)

This product was isolated along with **6b** from hydrogenation of a mixture of **8a** and **8b**.

Example 17

3-Butyl-3-ethyl-6-hydroxy-5-phenylthio-2,3,6,5-tetrahydro-benzothiepine-1,1-dioxide (21)

A mixture of 25 mg (0.085 mmole) of **19b**, 0.27 g (2.7 mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium carbonate, and 4 mL of DMF was stirred at room temperature under N_2 for 19 h. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed successively with 10% NaOH and brine, dried over $MgSO_4$, and concentrated in vacuo to give 0.19 g of semisolid which contain substantial amounts of diphenyl disulfide. This material was purified by HPLC (5% EtOAc-hexane) to remove diphenyl disulfide in the first fraction. The column was then eluted with 20% EtOAc-hexane to give 17 mg of a first fraction, 4 mg of a second fraction and 11 mg of a third fraction which were three different isomers of **21**, i.e. **21a**, **21b**, and **21c**, respectively, by ^1H NMR and mass spectra.

Example 18

Alternative Synthesis of 6c and 6d

A. Preparation from 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

Step 1. 2-((2-Benzoylphenylsulfonyl)methyl)-2-ethylhexanal (44)

To a solution of 9.0 g (0.025 mole) of compound **2** in 100 ml of methylene chloride was added 14.6 g (0.025 mol) of 50-60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h then was stirred with 200 ml of 1 M potassium carbonate and

filtered through Celite. The methylene chloride layer was washed twice with 300 ml of 1 M potassium carbonate, once with 10% sodium hydroxide and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene chloride solution was dried and concentrated in vacuo to give 9.2 g (95%)of semisolid. A portion (2.6 g) of this solid was purified by HPLC(10% ethyl acetate-hexane) to give 1.9 g of crystals, mp 135-136 °C

Step 2. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)

A solution of 50 g (0.13 mole) of crude 44 in 250 ml of methylene chloride was divided in two portions and charged to two Fisher-Porter bottles. To each bottle was charged 125 ml of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time but only 1 g of Pd/C was charged to the reaction mixture. The combined reaction mixture was filtered and concentrated in vacuo to give 46.8 g of 45 as brown oil.

Step 3. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)

To a solution of 27.3 g (73.4 mmole) of 45 in 300 ml of anhydrous THF cooled to 2 °C with an ice bath was added 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred for 20 min, quenched with 300 ml of 10% HCl and extracted with methylene chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give

24.7 g of yellow oil. Purification by HPLC (ethyl acetate-hexane) yielded 9.4 g of recovered **45** in the first fraction, 5.5 g (20%) of **6c** in the second fraction and 6.5 g (24%) of **6d** in the third fraction.

B. Preparation from 2-hydroxydiphenylmethane

Step 1. 2-mercaptodiphenylmethane (46)

To a 500 ml flask was charged 16 g (0.33 mol) of 60% sodium hydride oil dispersion. The sodium hydride was washed twice with 50 ml of hexane. To the reaction flask was charged 100 ml of DMF. To this mixture was added a solution of 55.2 g (0.3 mol) of 2-hydroxydiphenylmethane in 200 ml of DMF in 1 h while temperature was maintained below 30 °C by an ice-water bath. After complete addition of the reagent, the mixture was stirred at room temperature for 30 min then cooled with an ice bath. To the reaction mixture was added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl chloride at once. The ice bath was removed and the reaction mixture was stirred at room temperature for 18 h before being poured into 300 ml of water. The organic was extracted into 500 ml of toluene. The toluene layer was washed successively with 10% sodium hydroxide and brine and was concentrated in vacuo to give 78.6 g of a yellow oil which was 95% pure dimethyl *O*-2-benzylphenyl thiocarbamate. This oil was heated at 280-300 °C in a kugelrohhr pot under house vacuum for 30 min. The residue was kugelrohr distilled at 1 torr (180-280 °C). The distillate (56.3 g) was crystallized from methanol to give 37.3 g (46%) of the rearranged product dimethyl *S*-2-benzylphenyl thiocarbamate as a yellow solid. A mixture of 57 g (0.21 mole) of this yellow solid, 30 g of potassium hydroxide and 150 ml of methanol was stirred overnight then was concentrated in vacuo. The residue was diluted with 200 ml of water and extracted with ether. The aqueous layer was made acidic with concentrate HCl, The oily suspension was extracted into ether. The ether extract was dried over magnesium

sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of 2-mercaptodiphenylmethane as a yellow solid.

Step 2. 2-((2-Benzylphonylthio)methyl)-2-ethylhexanal (47)

A mixture of 60 g (03 mole) of yellow solid from step 1, 70 g (0.3 mole) of compound **1** from preparation 1, 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-methoxyethyl ether was held at reflux for 6 hr and concentrated in vacuo. The residue was triturated with 500 ml of water and 30 ml of concentrate HCl. The organic was extracted into 400 ml of ether. The ether layer was washed successively with brine, 10% sodium hydroxide and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2-5% ethyl acetate-hexane as eluent to give 2-((2-benzylphenylthio)methyl)-2-ethylhexanal **47** as a yellow syrup.

Step 3. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)

To a solution of 72.8 g (0.21 mole) of yellow syrup from step 2 in 1 liter of methylene chloride cooled to 10 °C was added 132 g of 50-60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50-60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered through Celite. The methylene chloride solution was washed twice with 1 liter of 1 M potassium carbonate then with 1 liter of brine. The methylene chloride layer was dried over magnesium sulfate and concentrated to 76 g of 2-((2-benzylphenylsulfonyl)methyl)-2-ethylhexanal **45** as a syrup.

Step 4. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)

Reaction of **45** with potassium t-butoxide according to the procedure in step 3 of procedure A gave pure **6c** and **6d** after HPLC.

Example 19

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26)

Step 1. Preparation of 2-((2-benzoyl-4-methoxy phenylthio)methyl)-2-ethylhexanal (22)

2-Hydroxy-4-methoxybenzophenone was converted to the dimethyl *O*-2-benzoyphenyl thiocarbamate by methods previously described in example 18. The product can be isolated by recrystallization from ethanol. Using this improved isolation procedure no chromatography was needed. The thermal rearrangement was performed by reacting the thiocarbamate(5 g) in diphenyl ether at 260 °C as previously described. The improved isolation procedure which avoided a chromatography step was described below.

The crude pyrolysis product was then heated at 65 °C in 100 ml of methanol and 100 ml of THF in the presence of 3.5 g of KOH for 4 h. After removing THF and methanol by rotary evaporation the solution was extracted with 5 % NaOH and ether. The base layer was acidified and extracted with ether to obtain a 2.9 g of crude thiophenol product. The product was further purified by titrating the desired mercaptan into base with limited KOH. After acidification and extraction with ether pure 2-mercapto-4-methoxybenzophenone (2.3 g) was isolated.

2-mercapto-4-methoxybenzophenone can readily be converted to the 2-((2-benzoyl-4-

methoxyphenylthio)methyl)-2-ethylhexanal **(22)** by reaction with 2-ethyl-2-(mesyloxymethyl)hexanal **(1)** as previously described.

Step 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (23)

Substrate **22** was readily oxidized to **2-((2-benzoyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (23)** as described in example 18.

Step 3. 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (24)

Sulfone **23** was then reduced to **2-((2-benzyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (24)** as described in example 18.

Step 4. (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26)

A 3-neck flask equipped with a powder addition funnel,thermocouple and nitrogen bubbler was charged with 19.8 g (0.05 mole) of sulfone **24** in 100 ml dry THF. The reaction was cooled to -1.6 °C internal temperature by means of ice/salt bath. Slowly add 5.61 g (0.05 mole) of potassium t-butoxide by means of the powder addition funnel. The resulting light yellow solution was maintained at -1.6 °C. After 30 min reaction 400 ml of cold ether was added and this solution was extracted with cold 10 % HCl. The acid layer was extracted with 300 ml of methylene chloride. The organic layers were combined and dried over magnesium sulfate and after filtration stripped to dryness to obtain 19.9 g of product. ^{1}H nmr and glpc indicated a 96% conversion to a 50/50 mixture of **25** and

26. The only other observable compound was 4% starting sulfone 24.

The product was then dissolved in 250 ml of 90/10 hexane/ethyl acetate by warming to 50 °C. The solution was allowed to cool to room temperature and in this way pure 26 can be isolated. The crystallization can be enhanced by addition of a seed crystal of 26. After 2 crystallizations the mother liquor which was now 85.4% 25 and has a dry weight of 8.7 g. This material was dissolved in 100 ml of 90/10 hexane/ethyl acetate and 10 ml of pure ethyl acetate at 40 C. Pure 25 can be isolated by seeding this solution with a seed crystal of 25 after storing it overnight at 0 C.

Example 20

(3a,4a,5a) 3-Butyl-3-ethyl-4,8-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (27)

In a 25 ml round bottomed flask, 1 g of 26(2.5 mmoles) and 10 ml methylene chloride were cooled to - 78 °C with stirring. Next 0.7 ml of boron tribromide(7.5 mmole) was added via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 6 h. The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water.The organic layer was dried over magnesium sulfate. The product (0.88g) 27 was characterized by NMR and mass spectra.

Example 21

General Alkylation of phenol 27

A 25 ml flask was charged with 0.15 g of 27(0.38 mmole), 5 ml anhydrous DMF, 54 mg of potassium carbonate(0.38 mmole) and 140 mg ethyl iodide (0.9 mmole). The reaction was stirred at room temperature overnight.The reaction was diluted with 50 ml ethyl ether and washed with water (25 ml) then 5% NaOH (20 ml) and then sat. NaCl. After stripping off the solvent

the ethoxylated product 28 was obtained in high yield. The product was characterized by NMR and mass spectra. This same procedure was used to prepare products listed in table 1 from the corresponding iodides or bromides. For higher boiling alkyl iodides and bromides only one equivalent of the alkyl halide was used.

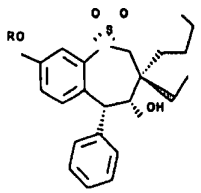


Table 1

Compound No.	R
27	H
26	Me
28	Et
29	hexyl
30	Ac
31	(CH2)6-N-pthalimide

Example 22

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (37) and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiopine-1,1-dioxide (38)

Step 1. Preparation of 2-chloro-5-nitrodiphenylmethane (32)

Procedure adapted from reference :Synthesis -Stuttgart 9 770-772 (1986) Olah G. Et al

Under nitrogen, a 3 neck flask was charged with 45 g (0.172 mole) of 2-chloro-5-nitrobenzophenone in 345 ml methylene chloride and the solution was cooled to ice/water temperature. By means of an additional funnel, 150 g(0.172 mole) of trifluoromethane sulfonic acid in 345 ml methylene chloride was added slowly. Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride was added dropwise to the chilled solution. Both addition steps(trifluoromethane sulfonic acid and triethylsilane)were repeated. After the additions were completed the reaction was allowed to slowly warm up to room temperature and stirred for 12 h under nitrogen. The reaction mixture was then poured into a chilled stirred solution of 1600 ml of saturated sodium bicarbonate. Gas evolution occurred. Poured into a 4 liter separatory funnel and separated layers. The methylene chloride layer was isolated and combined with two 500 ml methylene chloride extractions

of the aqueous layer. The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give 39 g product. Structure **32** was confirmed by mass spectra and proton and carbon NMR.

Step 2. Preparation of 2-((2-benzyl-4-nitrophenylthio)methyl)-2-ethylhexanal (33)

The 2-chloro-5-nitrodiphenylmethane product **32** (40 g, 0.156 mole) from above was placed in a 2 liter 2 neck flask with water condenser. Next 150 ml DMSO and 7.18 g (0.156 mole) of lithium sulfide was added and the solution was stirred at 75 °C for 12 h. The reaction was cooled to room temperature and then 51.7 g of mesylate IV was added in 90 ml DMSO. The reaction mixture was heated to 80 °C under nitrogen. After 12 h monitored by TLC and added more mysylate if necessary. Continued the reaction until the reaction was completed. Next the reaction mixture was slowly poured into a 1900 ml of 5% acetic aqueous solution with stirring, extracted with 4 X 700 ml of ether, and dried over MgSO4. After removal of ether, 82.7 g of product was isolated. The material can be further purified by silica gel chromatography using 95% hexane and 5 % ethyl acetate. If pure mysylate was used in this step there was no need for further purification. The product **33** was characterized by mass spectra and NMR.

Step 3. Oxidation of the nitro product 33 to the sulfone 2-((2-benzyl-4-nitrophenylsulfonyl)methyl)-2-ethylhexanal (34)

The procedure used to oxidize the sulfide **33** to the sulfone **34** has been previously described.

Step 4. Reduction of 34 to 2-((2-benzyl-4-hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (35)

A 15 g sample of **34** was dissolved in 230 ml of ethanol and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt.% Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate **34** was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product **35** was isolated by filtering off the Pd/C and then stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

Step 5. Preparation of the 2-((2-benzyl-4-*N,O*-di-(t-butoxy-carbonyl)hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (36).

A 13.35 g sample of **35** (0.0344 mole) in 40 ml of dry THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of di-t-butyl dicarbonate in 7 ml THF. Heated at 60 °C overnight. Striped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.

The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product **36** was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.

Step 6. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiopine-1,1-dioxide (37) and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiopine-1,1-dioxide (38)

A 250ml 3-neck round bottomed flask was charged with 4 g of **36** (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78 °C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide(20.4 mmoles) with stirring and maintaining a -78 °C reaction temperature. After 1 h at -78 °C the addition of base was completed and the temperature was brought to -10 °C by means of a

ice/salt bath. After 3 h at -10 °C, only trace **36** remained by TLC. Next add 35 ml of deionized water to the reaction mixture at -10 °C and stirred for 5 min. Striped off most of the THF and added to separatory funnel and extracted with ether until all of the organic was removed from the water phase. The combined ether phases were washed with saturated NaCl and then dried over sodium sulfate. The only products by TLC and NMR were the two BOC protected isomers of **37 and 38**. The isomers were separated by silica gel chromatography using 85% hexane and 15 % ethyl acetate; **BOC-37** (0.71 g) and **BOC- 38** (0.78 g).

Next the BOC protecting group was removed by reacting 0.87 g of **BOC-38** (1.78 mmoles) with 8.7 ml of 4 M HCl (34.8 mmoles)in dioxane for 30 min. Next added 4.74 g of sodium acetate (34.8 mmoles) to the reaction mixture and 16.5 ml ether and stirred until clear. After transferring to a separatory funnel extracted with ether and water and then dried the ether layer with sodium sulfate. After removing the ether, 0.665 g of **38** was isolated. Isomer **37** could be obtained in a similar procedure.

Example 23

(3a,4a,5a) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiopino-1,1-dioxido (60) and (3a,4b,5b) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiopino-1,1-dioxido (61)

Step 1. 2-((2-Benzyl-4-(n-hexylamino)phonylsulfonyl)methyl)-2-ethylhexanal (39)

In a Fischer porter bottle weighed out 0.5 g of **34** (1.2 mmoles) and dissolved in 3.8 ml of ethanol under nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexanal. Seal and pressure to 50 psi of hydrogen gas. Stirred for 48 h. After filtering off the catalyst and removing the solvent by rotary evaporation **39** was

isolated by column chromatography (0.16 g) using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. The product was characterized by NMR and mass spectra.

Step 2. (3a,4a,5a) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (40) and (3a,4b,5b) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (41)

A 2-neck, 25 ml round bottomed flask with stir bar was charged with 0.158 g **39** (0.335 mmole) and 5 ml anhydrous THF under nitrogen. Cool to -10 °C by means of a salt/water bath. Slowly add 0.113 g of potassium tert butoxide (0.335 mmole). After 15 min at -10 °C all of the starting material was consumed by TLC and only the two isomers **40** and **41** were observed. Next added 5 ml of chilled 10% HCl and stirred at -10 °C for 5 min. Transferred to a separatory funnel and extract with ether. Dried over sodium sulfate. Proton NMR of the dried product (0.143 g) indicated only the presence of the two isomers **40** and **41**. The two isomers were separated by silica gel chromatography using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. **40** (53.2 mg); **41**(58.9 mg).

Example 24

Quaternization of amine substrates 40 and 41

Amine products such as **40** and **41** can be readily alkylated to quaternary salts by reaction with alkyl halides. For example **40** in DMF with 5 equivalents of methyl iodide in the presence of 2,6 dimethyl lutidine produces the dimethylhexylamino quaternary salt.

Example 25

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (42)

In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of **6d** , 0.67 g of mercuric triflate were dissolved in 20 ml of dry methylene chloride with stirring. Next 0.34 g of Iodine was added and the solution was stirred at room temperature for 30 h. The reaction was then diluted with 50 ml methylene chloride and washed with 10 ml of 1 M sodium thiosulfate; 10 ml of saturated KI ; and dried over sodium sulfate. See Tetrahedron, Vol.50, No. 17, pp 5139-5146 (1994) Bachki, F. Et al.Mass spectrum indicated a mixture of **6d** , mono iodide **42** and a diiodide adduct. The mixture was separated by column chromatography and **42** was characterized bt NMR and mass spectra.

Example 26

(3a,4b,5b) 3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (43)

A 0.1 g sample of **42** (0.212 mmole), 2.5 ml dry methanol, 38 µl triethylamine (0.275 mmole) , 0.3 ml toluene and 37 mg of palladium chloride (0.21 mmole) was charged to a glass lined mini reactor at 300 psi carbon monoxide. The reaction was heated at 100 °C overnight. The catalyst was filtered and a high yield of product was isolated.
The product was characterized by NMR and mass spectra.

Note the ester functionalized product **43** can be converted to the free acid by hydrolysis.

Example 27

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-

methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)

Step 1. 2-Mercapto-5-methoxybenzophenone (50)

Reaction of 66.2 g of 4-methoxythiophenol with 360 ml of 2.5 N n-butyllithium, 105 g of tetramethylethylenediamine and 66.7 g of benzonitrile in 600 ml cyclohexane according to the procedure in WO 93/16055 gave 73.2 g of brown oil which was kugelrohr distilled to remove 4-methoxythiophenol and gave 43.86 g of crude **50** in the pot residue.

Step 2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (51)

Reaction of 10 g (0.04 mole) of crude **50** with 4.8 g (0.02 mole)of mesylate **1** and 3.2 ml (0.23 mole) of triethylamine in 50 ml of diglyme according to the procedure for the preparation of **2** gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-hexane) to give 1.7 g (22%) of **51**.

Step 3. 2-((2-Benzoyl-4-methoxyphenylsulfonyl)methyl)-2-ethyl-hexanal (52)

A solution of 1.2 g (3.1 mmoles) of **51** in 25 ml of methylene chloride was reacted with 2.0 g (6.2 mmoles) of 50-60% MCPBA according to the procedure of step 2 of procedure A in example 18 gave 1.16 g (90%) of **52** as a yellow oil.

Step 4. 2-((2-Benzyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (53)

Hydrogenation of 1.1 g of **52** according to the procedure of step 3 of procedure A of example 18 gave **53** as a yellow oil (1.1 g).

Step 5. (3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)

A solution of 1.1 g of **53**, 0.36 g of potassium t-butoxide and 25 ml of anhydrous THF was held at reflux for 2 h and worked up as in step 4 of procedure A of example 18 to give 1.07 g of a crude product which was purified by HPLC to give 40 mg (4%) of **48** as crystals, mp 153-154 °C and 90 mg (8%) of **49** as solid, mp 136-140 °C.

Example 28

5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)

Step 1. 1-(Hydroxymethyl)-cyclohexanecarboxaldehyde (54)

To a cold (0 °C) mixture of 100 g (0.891 mole) of cyclohexanecarboxaldehyde, 76.5 g of 37% of formaldehyde in 225 ml of methanol was added dropwise 90 ml of 1 N Sodium hydroxide in 1 h. The reaction mixture was stirred at room temperature over 48 then was evaporated to remove methanol. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 75 g (59.7%) of thick oil. Proton NMR and mass spectra were consistent with the product.

Step 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde (55)

To a cold (0 °C) mixture of alcohol **54** (75 g, 0.54 mole) and 65.29 g (0.57 mole) of methanesulfonyl chloride in 80 ml of methylene chloride was added a solution of pyridine (47.96 g, 0.57 mole) in 40 ml of methylene

chloride. The reaction mixture was stirred at room temperature for 18 h then quenched with water, acidified with conc. HCl and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 91.63 g (77.8%) of thick oil. Proton NMR and mass spectra were consistent with the product.

Step 3. 1-((2-Benzoylphenylthio)methyl)cyclohexanecarboxaldehyde (56)

A mixture of 69 g (0.303 mole) of 2-mercaptobenzophenone, 82 g (0.303 mole) of mesylate **55**, 32 g of triethylamine, and 150 ml of diglyme was stirred and held at reflux for 24 h. The mixture was cooled, poured into dil. HCl and extracted with methylene chloride. The organic layer was washed with 10% NaOH, water, brine, and dried over sodium sulfate and concentrated under vacuum to remove excess diglyme. This was purified by silica gel flush column (5% EtOAc: Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton NMR and mass spectra were consistent with the product.

Step 4. 5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)

To a mixture of 6.19 g of zinc dust and 100 ml of dry DME was added $TiCl_4$(16.8 g, 0.108 mole) . The reaction mixture was heated to reflux for 2 h. A solution of compound **56** (8.3 g, 0.023 mole) in 50 ml of DME was added dropwise to the reaction mixture in 1 h and the mixture was held at reflux for 18 h. The mixture was cooled, poured into water and extracted with ether. The organic layer was washed with water, brine, and dried over sodium sulfate, filtered through celite and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white

solid, mp 90-91 °C. Proton and carbon NMR and mass spectra were consistent with the product.

Example 29

8b-Phenyl-1a,2,3,8b-tetrahydrospiro(benzothiepino[4,5-b]oxirene-2,1'-cyclohexane)-4,4-dioxide (58)

To a solution of **57** (4.6 g, 15 mmole) in 50 ml chloroform under nitrogen was added 55% MCPBA (16.5 g, 52.6 mmole) portionwise with spatula. The reaction was held at reflux for 18 h and washed with 10% NaOH(3X), water, brine, and dried over sodium sulfate and concentrated under vacuum to give 5 g of crude product. This was recrystallized from Hexane/EtOAc to give 4.31 g (81%) of yellow solid, mp 154-155 °C. Proton and carbon NMR and mass spectra were consistent with the product.

Example 30

trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (59)

A mixture of 0.5 g (1.4 mmoles) of **58** , 20 ml of ethanol,10 ml of methylene chloride and 0.4 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to dryness. The residue was purified by HPLC (10% EtOAc-Hexane, 25% EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was a trans isomer. The second fraction gave 200 mg of solid which was impure cis isomer.

Example 31

cis-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (60)

To a solution of 0.2 g (0.56 mmole) of **59** in 20 ml of CH_2Cl_2, was added 8 g of 50% NaOH and one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst. The reaction mixture was stirred for 10 h at room temperature. Twenty g of ice was added to the mixture and the mixture was extracted with CH_2Cl_2 (3x10 ml) washed with water, brine and dried over $MgSO_4$ and concentrated in vacuo to recover 0.15 g of crude product. This was recrystallized from Hexane/EtOAc to give 125 mg of white crystal, mp 209-210 °C . Proton and carbon NMR and mass spectra were consistent with the product.

Example 32

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (61), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (62)

To a solution of 0.5 g (1.47 mmole) of compound **47** in 5 ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred at room temperature for 18 h and quenched with 10 ml of 10% HCl. The organic was extracted into methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by HPLC (2% EtOAc-hexane) to give 47 mg of **61** in the second fraction and 38 mg of **62** in the third fraction. Proton NMR and mass spectra were consistent with the assigned structures.

Example 33

(3a,4a,5a) 3-Butyl-3ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (63) and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide(64)

An autoclave was charged with 200 mg of **37** in 40 cc ethanol and .02 g 10 % Pd/C. After purging with

nitrogen the clave was charged with 100 psi hydrogen and heated to 55 C. The reaction was monitored by TLC and mass spec and allowed to proceed until all of **37** was consumed. After the reaction was complete the catalyst was filtered and the solvent was removed in vacuo and the only observable product was amine **63**. This same procedure was used to produce **64** from **38**.

Example 34

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (65), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (66). Alkylation of e-methoxyphenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-methoxybenzyl)phenol in 35% yield. This material was converted to compound 65, mp 138.5-141.5 °C, and compound 66, mp 115.5-117.5 °C, by the procedure similar to that in Example 18 method B.

Example 35

(3a,4a,5a) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (67), and (3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (68). Alkylation of 4-methoxyphenol with 3-(trifluoromethyl)benzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-(trifluoromethyl)benzyl)phenol. This material was converted to compound 67, mp 226.5-228 °C, and compound 68, mp 188-190°C, byu the procedure similar to that in Example 18 method B.

Example 36

(3a,4a,5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (69), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (70).

Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(4'-fluorobenzyl)phenol. This material was converted to compound 69 and compound 70 by the procedure similar to that in Example 18 method B.

Example 37

(3a,4a,5a) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (71), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (72).

Alkylation of 4-methoxyphenol with 3-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-fluorobenzyl)phenol. This material was converted to compound 71 and compound 72 by the procedure similar to that in Example 18 method B.

Example 38

(3a,4a,5a) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).

Alkylation of 4-methoxyphenol with 2-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to

compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

Example 39

(3a,4a,5a) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (75), and (3a,4b,5b) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).

Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.

Example 40

(3a,4a,5a) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (77), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (78).

Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230 °C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

Example 41

(3a,4a,5a) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and (3a,4b,5b) 3-Butyl-3-ethyl-7-fluoro-

40hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (80).

Alkylation of 4-fluorophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-methoxybenzyl)phenol. This material was converted to compound 79, as a solid and compound 80, mp 153-155 °C, by the procedure similar to that in Example 18 method B.

Example 42

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (81).

A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was dilute with ether and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20% ethyl acetate in hexanes). The first fraction was impure (3a,4a,5a) 3-butyl-3-ethyl-4-hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide. The second fraction was compound 81, mp 185-186.5 °C.

Example 43

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-pyrrolidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (82).

A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml of pyrrolidine was held at reflux for 1 h. The reaction mixture was diluted with ether and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was

crystallized from ether-hexanes to give compound 82, mp 174.5-177 °C.

Example 44

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-morpholinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (83).

A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g (56 mmol) of morpholine was held at reflux for 2 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over M_gSO_4. The ether solution was concentrated in vacuo. The residue was recrystallized from ether-hexanes to give compound 83, mp 176.5-187.5 °C.

Example 45

(3a,4a,5a) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (84), and (3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (85).

Alkylation of 4-methylphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methyl-2-(4'-fluorobenzyl)phenol). This material was converted to compound 84 and compound 85 by the procedure similar to that in Example 18 method B.

Example 46

(3a,4b,5b) 3-Butyl-3-ethyl-4-hydroxy-5-(4'-hydroxyphenyl)-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (86), and (3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (87).

To a solution of 0.52 (1.2 mmol) of compound 66 in 20 ml of methylene chloride was added 1.7 g (6.78 mmol) of born tribromide. The reaction mixture was cooled to -78 °C and was stirred for 4 min. An additional 0.3 ml of boron tribromide was added to the reaction mixture and the reaction mixture was stirred at -78 °C for 1 h and quenced with 2 N HCl. The organic was extracted into ether. The ether layer was washed with brine, dried over M_gSO_4, and concentrated in vacuo. The residue (0.48 g) was purified by HPLC (30% ethyl acetate in hexanes). The first fraction was 0.11 g of compound 86 as a white solid, mp 171.5-173 °C. The second fraction was crystallized from chloroform to give 0.04 g of compound 87 as a white solid, mp 264 °C (dec).

Example 47

(3a,4b,5b) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (88).

Reaction of compound 70 with excess boron tribromide at room temperature and worked up as in Example 46 gave compound 88 after an HPLC purification.

Example 48

(3a,4b,5b) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-azetidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (89).

A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 g (35 mmol) of aztidine was held at reflux for 3 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over MgSO4. The ether solution was concentrated on a steam bath. The separated crystals were filtered to give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.

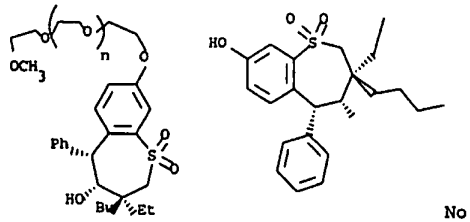
Example 49

(3a,4a,5a) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (90). (3a,4b,5b) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (91).

A mixture of 0.4 g (0.95 mmol) of compound 79, 0.08 g (1.14 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at 60 °C for 2 h. An additional 1.4 mmol of sodium methanethiolate was added to the reaction mixture and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was triturated with 100 ml of water and extracted methylene chloride. The methylene chloride water mixture was filtered through Celite and the methylene chloride layer was dried over M_gSO_4 and concentrated in vacuo. The first fraction (0.1 g) was compound 90, mp 117-121 °C. The second fraction (0.16 g) was compound 91, mp 68-76 °C.

Example 50

Preparation of polyethyleneglycol functionalized benzothiepine A.



No. 141

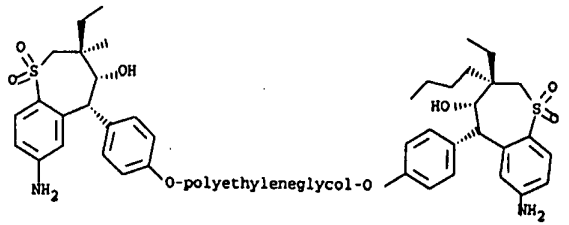
No.136

A 50 ml rb flash under a nitrogen atmospherewas charged with 0.54 g of M-Tres-5000 (Polyethyleneglycol Tresylate [methoxy-PEG-Tres,MW 5000] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.055 g Compound No. 136, 0.326 C_2CO_3 and 2cc anhydrous acetonitrile. The reaction was stirred at 30 C for 5 days and then the solution was filtered to remove salts. Next, the acetonitrile was removed under vacuum and the product was dissolved in THF and then precipitated by addition of hexane. The polymer precipitate was isolate by filtration from the solvent mixture (THF/hexane). This precipitation procedure was continued until no Compound No. 136 was detected in the precipitated product (by TLC SiO2). Next, the polymer precipitate was dissolved in water and filtered and the water soluble polymer was dialyzed for 48 hours through a cellulose dialysis tube (Spectrum® 7 ,45 mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried. The NMR was consistent with the desired product A and gel permeation

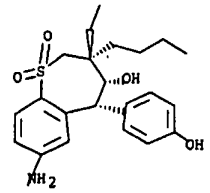
chromatography indicated the presence of a 4500 MW polymer and also verified that no free Compound No. 136 was present. This material was active in the IBAT in vitro cell assay.

Example 51

Preparation of Compound 140



No. 140

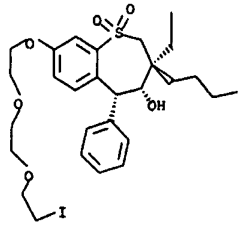


No. 111

A 2-necked 50 ml round bottom Flask was charged with 0.42g of Tres-3400 (Polyethyleneglycol Tresylate [Tres-PEG-Tres,MW 3400] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.1 potassium carbonate, 0.100g of Compound No. 111 and 5 ml anhydrous DMF. Stir for 6 days at 27 °C. TLC indicated the disappearance of the starting

Compound No. 111. The solution was transferred to a separatory funnel and diluted with 50 cc methylene chloride and then extracted with water. The organic layer was evaporated to dryness by means of a rotary evaporator. Dry wgt. 0.4875 g. Next, the polymer was dissolved in water and then dialyzed for 48 hours at 40 °C through a cellulose dialysis tube (spectrum® 7 ,45mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried 0.341 g). NMR was consistent with the desired product B.

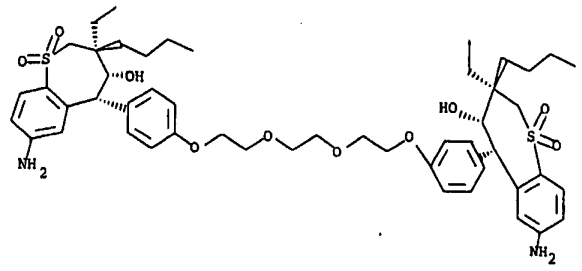
Example 52



No. 134

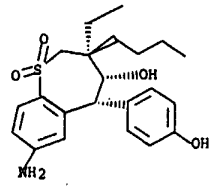
A 10 cc vial was charged with 0.21 g of Compound No. 136 (0.5mmoles), 0.17g (1.3 mmoles)potassium carbonate, 0.6g (1.5 mmoles) of 1,2-bis-(2-iodoethoxy)-ethane and 10 cc DMF. The reaction was stirred for 4 days at room temperature and then worked up by washing with ether/water. The ether layer was stripped to dryness and the desired product Compound No. 134 was isolated on a silica gel column using 80/20 hexane ethyl acetate.

Example 53



No. 112

Example 54

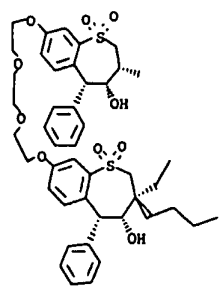


No. 113

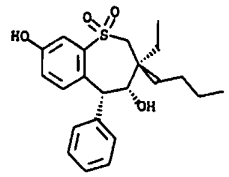
A two necked 25 ml round bottom Flask was charged with 0.5g (1.24mmoles) of 69462, 13 mls of anhydrous DMF, 0.055g of 60% NaH dispersion and 0.230g (0.62 mmoles) of 1,2-Bis [2-iodoethoxylethane) at 10 °C under nitogen. Next, the reaction was slowly heated to 40 °C. After 14 hours all of the Compound No. 113 was consumed and the reaction was cooled to room temperature and extracted with ether/water. The ether layer was evaporated to dryness and then chromatographed on Silicage (80/20 ethyl

acetate/hexane). Isolated Compound No. 112 (0.28 g) was characterized by NMR and mass spec.

Example 55



No. 135



No. 136

In a 50 ml round bottom Flask, add 0.7g (1.8 mmoles) of Compound No. 136, 0.621g of potassium carbonate, 6 ml DMF, and 0.33g of 1,2-Bis [2-iodoethoxylethane]. Stir at 40 °C under nitrogen for 12 hours. The workup and isolation was the same procedure for Compound No. 112.

Examples 56 and 57 (Compound Nos. 131 and 137)

The compositions of these compounds are shown in Table 3.

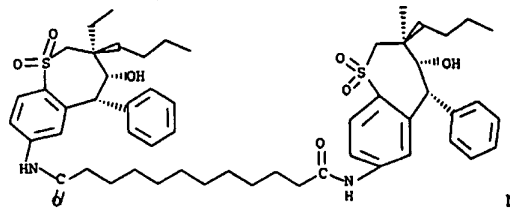
The same procedure as for Example 55 except appropriate benzothiepine was used.

Example 58 (Compound No. 139)

The composition of this compound is shown in Table 3.

Same procedure as for Example 55 with appropriate benzothiepine 1,6 diiodohexane was used instead of 1,2-Bis [2-iodoethoxylethane].

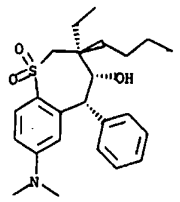
Example 59 (Compound No. 101)



No.101

This compound is prepared by condensing the 7-NH_2 benzothiepine with the 1,12-dodecane dicarboxylic acid or acid halide.

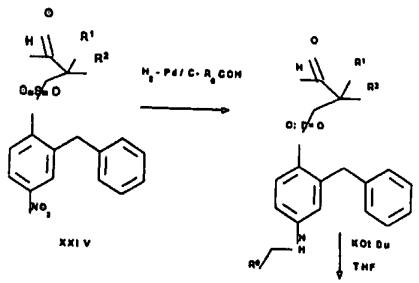
Example 60 (Compound No. 104)

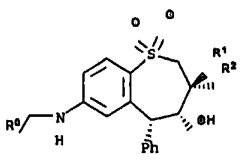


No. 104

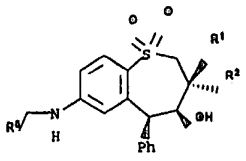
2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 5). Reduction of the sulfone-aldehyde XXV formaldehyde and 100 psi hydrogen and 55 C for 12 hours catalyzed by palladium on carbon in the same reaction vessel yields the substituted dimethylamine derivative XXVIII. Cyclization of XXVII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention Compound No. 104.

Scheme 6



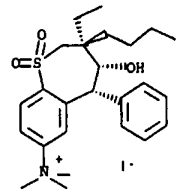


XXI Xc



XXI Xd

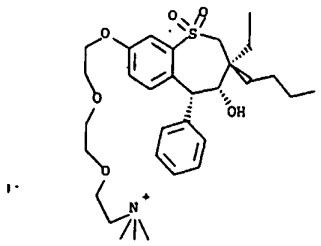
Example 61



No. 102

A 1 oz. Fisher-porter bottle was charged with 0.14 g (0.34 mmoles) of 70112, 0.97 gms (6.8 mmoles) of methyl iodide, and 7 ml of anhydrous acetonitrile. Heat to 50 °C for 4 days. The quat. Salt Compound No. 192 was isolated by concentrating to 1 cc acetonitrile and then precipitating with diethyl ether.

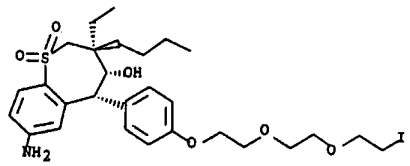
Example 62



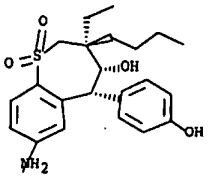
No. 125

A 0.1 g (0.159 mmoles) sample of Compound No. 134 was dissolved in 15 ml of anhydrous acetonitrile in a Fischer-porter bottle and then trimethylamine was bubbled through the solution for 5 minutes at 0 °C and then capped and warmed to room temperature. The reaction was stirred overnight and the desired product was isolated by removing solvent by rotary evaporation.

Example 63 (Compound No. 295)



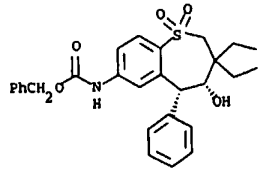
No. 295



No. 113

Sodium Hydride 60% (11 mg, 0.27 mmoles) in 1 cc of acetonitrile at 0 °C was reacted with 0.248 mmoles (.10 g) of Compound No. 54 in 2.5cc of acetonitrile at 0 °C. Next, 0.(980g 2.48 mmoles) of 1,2-Bis [2-iodoethoxylethane]. After warming to room temperature, stir for 14 hours. The product was isolated by column chromatography.

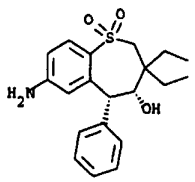
Example 64 (Compound No. 286)



No. 286

Following a procedure similar to the one described in Example 86, infra (see Compound No. 118), the title compound was prepared and purified as a colorless solid; mp 180-181 °C; ^{1}H NMR ($CHCl_3$) d 0.85 (t, J = 6 Hz, 3H_, 0.92 (t, J = 6 Hz, 3H), 1.24-1.42 (m, 2H), 1.46-1.56 (m, 1H), 1.64-1.80 (m, 1H), 2.24-2.38 (m, 1H), 3.15 (AB, J_{AB} = 15 Hz, Dv = 42 Hz, 2H), 4.20 (d, J = 8 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.46 (s, 1H), 6.68 (s, 1H), 7.29-7.51 (m, 10H), 7.74 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H). FABMS m/z 494 (M+H), HRMS calcd for (M+H) 494.2001, found 494.1993. Anal. Calcd. for $C_{28}H_{31}NO_5S$: C, 68.13; H, 6.33; N, 2.84. Found: C, 68.19; H, 6.56; N, 2.74.

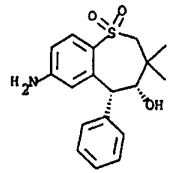
Example 65 (Compound No. 287)



No. 287

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless solid: mp 245-246 °C, ^{1}H NMR ($CDCl_3$) d 0.84 (t, J = 6 Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.28, (d, J = 8 Hz, 1H), 1.32-1.42 (m, 1H), 1.48-1.60 (m, 1H), 1.64-1.80 (m, 1H), 2.20-2.36 (m, 1H), 3.09 (AB, J_{AB} = 15 Hz, Dv = 42 Hz, 2H), 3.97 (bs, 2H), 4.15 (d, J = 8 Hz, 1H), 5.49 (s, 1H), 5.95 (s, 1H), 6.54 (d, J = 7 Hz, 1H), 7.29-7.53 (m, 5H), 7.88 (d, J = 8 Hz, 1H); ESMS 366 (M+Li). Anal. Calcd. for $C_{20}H_{33}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.54; H, 7.20; N, 3.69.

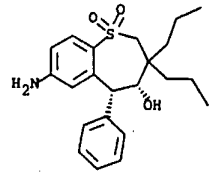
Example 66 (Compound No. 288)



No. 288

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified by silica gel chromatography to give the desired product as a colorless solid: mp 185-186°C; ^{1}H NMR ($CDCl_3$) d1.12 (s, 3H), 1.49 (s, 3H), 3.00 (d, J = 15 Hz, 1H), 3.28 (d, J = 15 Hz, 1H), 4.00 (s, 1H), 5.30 (s, 1H), 5.51 (s, 1H), 5.97 (s, 1H), 6.56 (dd, J = 2.1, 8.4 Hz, 1H), 7.31-7.52 (m, 5H), 7.89 (d, J = 8.4 Hz, 1H). MS (FAB+) (M+H) m/z 332.

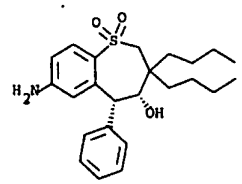
Example 67 (Compound No. 289)



No. 289

Following a procedure similar to the one described in Example 89 (see Compound No. 121), the title compound was prepared and purified by silica gel chromatography to give the desired product as a white solid: mp 205-206 °C; ^{1}H NMR ($CDCl_3$) d 0.80-0.95 (m, 6H), 1.10-1.70 (m, 7H), 2.15 (m, 1H), 3.02 (d, J = 15.3 Hz, 2H), 3.15 (d, J = 15.1 Hz, 2H), 3.96 (s, br, 2H), 4.14 (d, J = 7.8 Hz, 1H), 5.51 (s, 1H), 5.94 (d, J = 2.2, 1H), 6.54 (dd, J = 8.5, 2.2 Hz, 1H), 7.28-7.50 (m, 6H), 7.87 (d, J = 8.5 Hz, 1H). MS (FAB): m/z 388 (M+H).

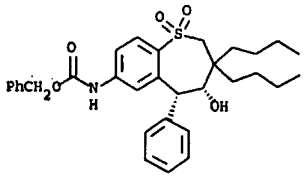
Example 68 (Compound No. 290)



No. 290

Following a procedure similar to the one described in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless solid: mp = 96-98 °C, ^{1}H NMR ($CDCl_3$) d 0.92 (t, J = 7 Hz, 6H), 1.03-1.70 (m, 11H), 2.21 (t, J = 8 Hz, 1H), 3.09 (AB, J_{AB} =- 18 Hz, Dv = 38 Hz, 2H), 3.96 (bs, 2H), 4.14 (d, J = 7 Hz, 1H), 5.51 (s, 1H), 5.94 (s, 1H), 6.56 (d, J = 9 Hz, 1H), 7.41-7.53 (m, 6H), 7.87 (d, J = 8 Hz, 1H); FABMS m/z 416 (M+H).

Example 69

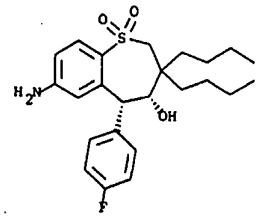


No. 291

Following a procedure similar to the one described in Example 86, infra (see Compound No. 118), the title compound was prepared and purified as a colorless solid: ^{1}H NMR ($CDCl_3$) d 0.91 (t, J = 7 Hz, 6H), 1.02-1.52 (m, 11H), 1.60-1.70 (m, 1H), 2.23 (t, J = 8 Hz,

1H), 3.12 (AB, J_{AB} = 18 Hz, Dv = 36 Hz, 2H), 4.18 (d, J = 7 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.43 (s, 1H), 6.65 (s, 1H), 7.29-7.52 (m, 10H), 7.74 (d, J = 9 Hz, 1H), 8.03 (d, J = 8 Hz, 1H); ESMS m/z 556 (M+Li).

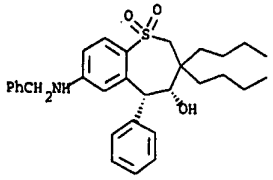
Example 70 (Compound No. 292)



No. 292

Following a procedure similar to the one descried in Example 89, infra (see Compound No. 121), the title compound was prepared and purified as a colorless solid: mp = 111-112.5°C, ^{1}H NMR ($CDCl_3$) d 0.90 (t, J = 8 Hz, 6H), 1.03-1.50 (m, 10H), 1.55-1.70 (m, 2H), 2.18 (t, J = 12 Hz, 2H), 3.07 (AB, J_{AB} = 15 Hz, Dv = 45 Hz, 2H), 4.09 (bs, 2H), 5.49 (s, 1H), 5.91 (s, 1H), 6.55 (d, J = 9 Hz, 1H), 7.10 (t, J = 7 Hz, 2H), 7.46 (t, J = 6 Hz, 2H), 7.87 (d, J = 9 Hz, 1H).

Example 71 (Compound No. 293)



No. 293

During the preparation of Compound No. 290 from Compound No. 291 using BBr_3, the title compound was

isolated: ^{1}H NMR ($CDCl_3$) d 0.85 (t, J = 6 Hz, 6H), 0.98-1.60 (m, 10H), 1.50-1.66 (m, 2H), 2.16 (t, J = 8 Hz, 1H), 3.04 (AB, J_{AB} = 15 Hz, Dv = 41 Hz, 2H), 4.08 (s, 1H), 4.12 (s, 1H), 5.44 (s, 1H), 5.84 (s, 1H), 6.42 (d, J = 9 Hz, 1H), 7.12 (d, J = 8 Hz, 2H), 7.16-7.26 (m, 10H), 7.83 (d, J = 8 Hz, 1H); ESMS m/z 512 (M+Li).

Example 72 (Compound No. 294)

Following a procedure similar to the one described in Example 60 (Compound No. 104), the title compound was prepared and purified as a colorless solid: ^{1}H NMR ($CDCl_3$) d 0.90 (t, J = 6 Hz, 6H), 1.05-1.54 (m, 9H), 1.60-1.70 (m, 1H), 2.24 (t, J = 8 Hz, 1H), 2.80 (s, 6H), 3.05 (AB, J_{AB} = 15 Hz, Dv = 42 Hz, 2H), 4.05-4.18 (m, 2H), 5.53 (s, 1H), 5.93 (s, 1H), 6.94 (d, J = 9 Hz, 1H), 7.27-7.42 (m, 4H), 7.45 (d, J = 8 Hz, 2H), 7.87 (d, J = 9 Hz, 1H); ESMS m/z 444 (M+H).

Structures of the compounds of Examples 33 to 72 are shown in Tables 3 and 3A.

Examples 73-79, 87, 88 and 91-102

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, compounds were prepared having the structures set forth in Table 3. The starting materials illustrated in the reaction schemes shown above were varied in accordance with principles of organic synthesis well known to the art to introduce the indicated substituents in the 4- and 5- positions (R^3, R^4, R^5, R^6) and in the indicated position on the benzo ring (R^7).

Structures of the the compounds produced in Examples 73-102 are set forth in Tables 3 and 3A.

Examples 80-84

Preparation of 115, 116, 111, 113

Preparation of 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.

In a 500 ml 2-necked rb flask weigh out 68.3 gms phosphorus pentachloride (0.328 mole 1.1 eq). Add 50 mls chlorobenzene. Slowly add 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole). Stir at room temp overnight under N2 then heat 1 hr at 50C.

Remove chlorobenzene by high vacuum. Wash residue with hexane. Dry wt=55.5 gms.

In the same rb flask, dissolve acid chloride (55.5 g 0.25 mole) from above with 100 mls anisole (about 3.4 eq). Chill solution with ice bath while purging with N2. Slowly add 40.3g aluminum chloride (1.2 eq 0.3 mole). Stir under N_2 for 24 hrs.

After 24 hrs, the solution was poured into 300 mls 1N HCl soln. (cold). Stir this for 15 min. Extract several times with diethyl ether. Extract organic layer once with 2% aqueous NaOH then twice with water. Dry organic layer with MgSO4, dry on vac line. Solid is washed well with ether and then ethanol before drying. Wt=34.57g (mixture of meta, ortho and para).

Elemental	theory	found
C	57.65	57.45
H	3.46	5.51
N	4.8	4.8
Cl	12.15	12.16

With the next step of the reduction of the ketone with trifluoromethane sulfonic aid and triethyl silane, crystallization with ethyl acetate/hexane affords pure 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.

4-Chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene was then reacted as specified in the synthesis of 117 and 118 from 2-chloro-4-nitrophenylmethane. From these procedures 115 and 116 can be synthesized. Compounds 111 and 113 can be synthesized from the procedure used to prepare compound 121.

Compound 114 can be prepared by reaction of 116 with ethyl mercaptan and aluminum trichloride.

Examples 85 and 86

Preparation of 117 and 118

2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 5).

The sulfone-aldehyde (31.8 g) was dissolved in ethanol/toluene and placed in a parr reactor with 100 ml toluene and 100 ml of ethanol and 3.2 g of 10% Pd/C and heated to 55 C and 100 psi of hydrogen gas for 14 hours. The reaction was then filtered to remove the catalyst. The amine product (.076 moles, 29.5 g) from this reaction was then reacted with benzyl chloroformate (27.4g) in toluene in the presence of 35 g of potassium carbonate and stirred at room

temperature overnight. After work up by extraction with water, the CBZ protected amine product was further purified by precipitation from toluene/hexane.

The CBZ protected amine product was then reacted with 3 equivalents of potassium t-butoxide in THF at 0 C to yield compounds 117 and 118 which were separated by silica gel column chromatography.

Examples 89 and 90

Preparation of 121 or 122

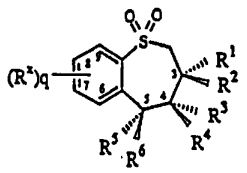
Compound 118 (.013 moles, 6.79g) is dissolved in 135 ml of dry chloroform and cooled to -78 C, next 1.85 ml of boron tribromide (4.9 g) was added and the reaction is allowed to warm to room temperature. Reaction is complete after 1.5 hours. The reaction is quenched by addition of 10% potassium carbonate at 0 C and extract with ether. Removal of ether yields compound 121. A similar procedure can be used to produce 122 from 117.

Examples 93-96

Compounds 126, 127, 128 and 129 as set forth in Table 3 were prepared substantially in the manner described above for compounds 115, 116, 111 and 113, respectively, except that fluorobenzene was used as a starting material in place of anisole.

TABLE 3

Specific compounds (#102-111,113-130,132-134,136,138,142-144,262-296)



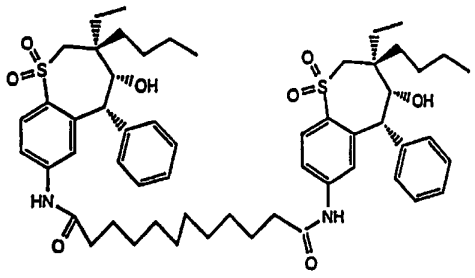
Ex.	Cp#	R^1	R^2	R^3	R^4	R^5	R^6	$(R^x)q$
61	102	Et-	n-Bu-	HO-	H-	Ph-	H-	I^-, 7-$(CH_3)_3N^+$-
73	103	n-Bu-	Et-	HO-	H-	Ph-	H-	I^-, 7-$(CH_3)_3N^+$-
60	104	Et-	n-Bu-	HO-	H-	Ph-	H-	7-$(CH_3)_2N$-
74	105	Et-	n-Bu-	HO-	H-	Ph-	H-	7-CH_3SO_2NH-
75	106	Et-	n-Bu-	HO-	H-	Ph-	H-	7-Br-CH_2-CONH-
76	107	n-Bu-	Et-	HO-	H-	p-n-$C_{10}H_{21}$--O-Ph-	H-	7-NH_2-
77	108	Et-	n-Bu-	HO-	H-	Ph-	H-	7-$C_5H_{11}CONH$-
78	109	Et-	n-Bu-	HO-	H-	p-n-$C_{10}H_{21}$--O-Ph-	H-	7-NH_2-
79	110	Et-	n-Bu-	HO-	H-	Ph-	H-	7-CH_3CONH-
80	111	n-Bu-	Et-	HO-	H-	p-HO-Ph-	H-	7-NH_2-
81	113	Et-	n-Bu-	HO-	H-	p-HO-Ph-	H-	7-NH_2-
82	114	Et-	n-Bu-	HO-	H-	p-CH_3O-Ph-	H-	7-NH_2-
83	115	n-Bu-	Et-	HO-	H-	p-CH_3O-Ph-	H-	7-NH-CBZ
84	116	Et-	n-Bu-	HO-	H-	p-CH_3O-Ph-	H-	7-NH-CBZ

85	117	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NH-CBZ
86	118	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NH-CBZ
87	119	Et-	n-Bu-	HO-	H-	Ph-	H-	7-$NHCO_2$-t-Bu
88	120	n-Bu-	Et-	HO-	H-	Ph-	H-	7-$NHCO_2$-t-Bu
89	121	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NH_2-
90	122	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NH_2-
91	123	Et-	n-Bu-	HO-	H-	Ph-	H-	7-n-C_6H_{13}-NH-
92	124	n-Bu-	Et-	HO-	H-	Ph-	H-	7-n-C_6H_{13}-NH-
62	125	Et-	n-Bu-	HO-	H-	Ph-	H-	I^-, 8-$(CH_3)_3N^+(CH_2CH_2O)_3$-
93	126	n-Bu-	Et-	HO-	H-	p-F-Ph-	H-	7-NH-CBZ
94	127	n-Bu-	Et-	HO-	H-	p-F-Ph-	H-	7-NH_2-
95	128	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH-CBZ
96	129	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH_2-
97	130	Et-	n-Bu-	HO-	H-	Ph-	H-	I^-, 8-$(CH_3)_3N^+C_6H_{12}O$-
98	132	Et-	n-Bu-	HO-	H-	Ph-	H-	8-phthalimidyl-$C_6H_{12}O$-
99	133	Et-	n-Bu-	HO-	H-	Ph-	H-	8-n-$C_{10}H_{21}$-
52	134	Et-	n-Bu-	HO-	H-	Ph-	H-	8- I-$(C_2H_4O)_3$-
100	136	Et-	n-Bu-	HO-	H-	Ph-	H-	8- HO-

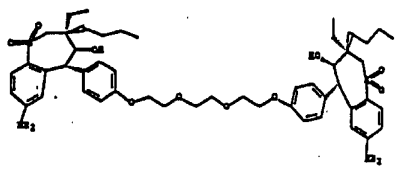
101	138	n-Bu-	Et-	HO-	H-	Ph-	H-	8- CH_3CO_2-
49	90	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-CH_3S-
49	91	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-CH_3S-
48	89	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-azetidine
34	66	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-CH_3O-
34	65	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-CH_3O-
35	68	Et-	n-Bu-	HO-	H-	m-CF_3-Ph-	H-	7-CH_3O-
35	67	Et-	n-Bu-	H-	HO-	H-	m-CF_3-Ph-	7-CH_3O-
46	87	Et-	n-Bu-	HO-	H-	m-HO-Ph-	H-	7-HO-
46	86	Et-	n-Bu-	HO-	H-	m-HO-Ph-	H-	7-CH_3O-
36	70	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH_3O-
36	69	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-CH_3O-
47	88	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-HO-
39	76	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-Br-
39	75	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-Br-
40	77	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-F-
40	78	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-F-
41	79	Et-	n-Bu-	H-	HO-	H-	m-CH_3O-Ph-	7-F-
41	80	Et-	n-Bu-	HO-	H-	m-CH_3O-Ph-	H-	7-F-
37	72	Et-	n-Bu-	HO-	H-	m-F-Ph-	H-	7-CH_3O-
38	73	Et-	n-Bu-	H-	HO-	H-	o-F-Ph-	7-CH_3O-
37	71	Et-	n-Bu-	H-	HO-	H-	m-F-Ph-	7-CH_3O-

38	74	Et-	n-Bu-	HO-	H-	o-F-Ph-	H-	7-CH_3O-
42	81	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH_3S-
45	85	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH_3-
45	84	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-CH_3-
44	83	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-morpholine.
43	82	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-pyrrolidine
64	286	Et-	Et-	HO-	H-	Ph-	H-	7-NH-CBZ
65	287	Et-	Et-	HO-	H-	Ph-	H-	7-NH_2-
66	288	CH_3-	CH_3-	HO-	H-	Ph-	H-	7-NH_2-
67	289	n-C_3H_7-	n-C_3H_7-	HO-	H-	Ph-	H-	7-NH_2-
68	290	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-NH_2-
69	291	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-NH-CBZ
70	292	n-Bu-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH_2-
71	293	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-$PhCH_2N$-
72	294	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-$(CH_3)_2N$-
63	295	Et-	n-Bu-	HO-	H-	p-I-$(C_2H_4O)_3$-Ph-	H-	7-NH_2-
102	296	Et-	n-Bu-	HO-	H-	I^-, p-$(CH_3)_3N^+(C_2H_4O)_3$-Ph-	H-	7-NH_2-

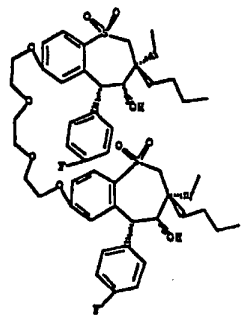
TABLE 3A
Bridged Benzothiephenes (#101,112,131,135,137,139-141)



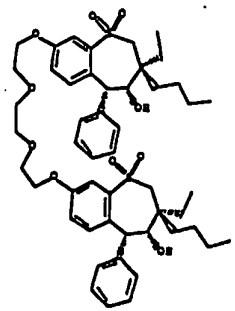
CPD #101 (Ex. 59)



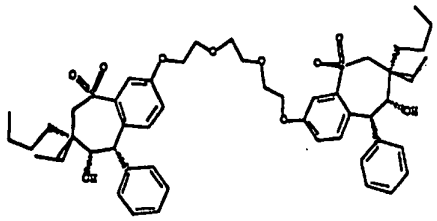
CPD #112 (Ex. 53)



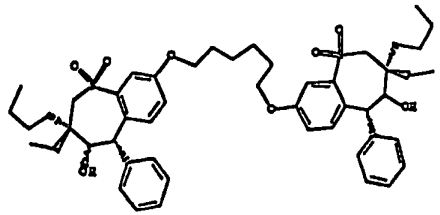
CPD#131 (Ex. 56)



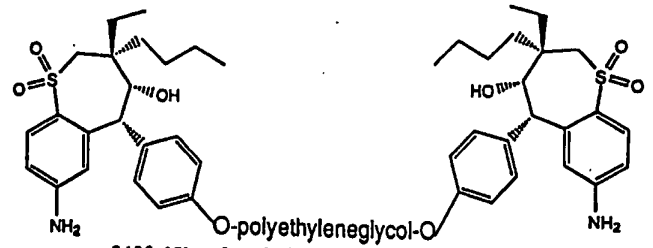
CPD #135 (Ex. 55)



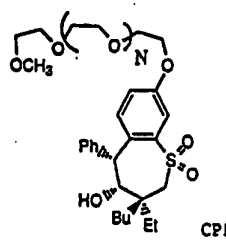
CPD #137 (Ex. 57)



CPD #139 (Ex. 58)



3400 MW polyethyleneglycol bridge CPD #140 (Ex. 51)

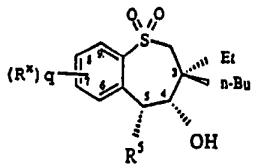


CPD #141 (Ex. 50)

Examples 104-231

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 4. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5-positions (R^3, R^4, R^5, R^6) and in the indicated position on the benzo ring (R^x).

TABLE 4
Alternative compounds #1 (#302-312, 314-430)



Cpd#	R^5	$(R^x)q$
302	p-F-Ph-	7-(1-aziridine)
303	p-F-Ph-	7-EtS-
304	p-F-Ph-	7-$CH_3S(O)$-
305	p-F-Ph-	7-$CH_3S(O)_2$-
306	p-F-Ph-	7-PhS-
307	p-F-Ph-	7-CH_3S- 9-CH_3S-
308	p-F-Ph-	7-CH_3O- 9-CH_3O-
309	p-F-Ph-	7-Et-
310	p-F-Ph-	7-iPr-
311	p-F-Ph-	7-t-Bu-
312	p-F-Ph-	7-(1-pyrazole)-
314	m-CH_3O-Ph	7-(1-azetidine)
315	m-CH_3O-Ph-	7-(1-aziridine)
316	m-CH_3O-Ph-	7-EtS-
317	m-CH_3O-Ph-	7-$CH_3S(O)$-
318	m-CH_3O-Ph-	7-$CH_3S(O)_2$-
319	m-CH_3O-Ph-	7-PhS-

320	m-CH_3O-Ph	7-CH_3S- 9-CH_3S-
321	m-CH_3O-Ph	7-CH_3O- 9-CH_3O-
322	m-CH_3O-Ph	7-Et-
323	m-CH_3O-Ph	7-iPr-
324	m-CH_3O-Ph	7-t-Bu-
325	p-F-Ph-	6-CH_3O- 7-CH_3O- 8-CH_3O-
326	p-F-Ph-	7-(1-azetidine) 9-CH_3-
327	p-F-Ph-	7-EtS- 9-CH_3-
328	p-F-Ph-	7-$CH_3S(O)$- 9-CH_3-
329	p-F-Ph-	7-$CH_3S(O)_2$- 9-CH_3-
330	p-F-Ph-	7-PhS- 9-CH_3-
331	p-F-Ph-	7-CH_3S- 9-CH_3-
332	p-F-Ph-	7-CH_3O- 9-CH_3-
333	p-F-Ph-	7-CH_3- 9-CH_3-
334	p-F-Ph-	7-CH_3O- 9-CH_3O-
335	p-F-Ph-	7-(1-pyrrole)
336	p-F-Ph-	7-(N)N'-methylpiperazine

337	p-F-Ph-	Ph-
338	p-F-Ph-	7-$CH_3C(=CH_2)$-
339	p-F-Ph-	7-cyclpropyl
340	p-F-Ph-	7-$(CH_3)_2NH$ -
341	p-F-Ph-	7-(N)-azetidine 9-CH_3S-
342	p-F-Ph-	7-(N-pyrrolidine) 9-CH_3S-
343	p-F-Ph-	7-$(CH_3)_2N$- 9-CH_3S-
344	m-CH_3O-Ph-	7-(1-pyrazole)
345	m-CH_3O-Ph-	7-(N)N'-methylpiperazine
346	m-CH_3O-Ph-	Ph-
347	m-CH_3O-Ph-	7-$CH_3C(=CH_2)$-
348	m-CH_3O-Ph-	7-cyclopropyl
349	m-CH_3O-Ph-	7-$(CH_3)_2NH$ -
350	m-CH_3O-Ph-	7-(N)-azetidine 9-CH_3S-
351	m-CH_3O-Ph-	7-(N-pyrrolidine)- 9-CH_3S-
352	m-CH_3O-Ph-	7-$(CH_3)_2N$- 9-CH_3S-
353	m-CH_3O-Ph-	6-CH_3O- 7-CH_3O- 8-CH_3O-
354	m-CH_3O-Ph-	7-(1-azetidine) 9-CH_3-

355	m-CH_3O-Ph-	7-EtS- 9-CH_3-
356	m-CH_3O-Ph-	7-$CH_3S(O)$- 9-CH_3-
357	m-CH_3O-Ph-	7-$CH_3S(O)_2$- 9-CH_3-
358	m-CH_3O-Ph-	7-PhS- 9-CH_3-
359	m-CH_3O-Ph-	7-CH_3S- 9-CH_3-
360	m-CH_3O-Ph-	7-CH_3O- 9-CH_3-
361	m-CH_3O-Ph-	7-CH_3- 9-CH_3-
362	m-CH_3O-Ph-	7-CH_3O- 9-CH_3O-
363	thien-2-yl	7-(1-aziridine)
364	thien-2-yl	7-EtS-
365	thien-2-yl	7-$CH_3S(O)$-
366	thien-2-yl	7-$CH_3S(O)_2$-
367	thien-2-yl	7-PhS-
368	thien-2-yl	7-CH_3S- 9-CH_3S-
369	thien-2-yl	7-CH_3O- 9-CH_3O-
370	thien-2-yl	7-Et-
371	thien-2-yl	7-iPr-
372	thien-2-yl	7-t-Bu-
373	thien-2-yl	7-(1-pyrrole)-
374	thien-2-yl	7-CH_3O-

375	thien-2-yl	7-CH_3S-
376	thien-2-yl	7-(1-azetidine)
377	thien-2-yl	7-Me-
378	5-Cl-thien-2-yl	7-(1-azetidine)
379	5-Cl-thien-2-yl	7-(1-aziridine)
380	5-Cl-thien-2-yl	7-EtS-
381	5-Cl-thien-2-yl	7-$CH_3S(O)$-
382	5-Cl-thien-2-yl	7-$CH_3S(O)_2$-
383	5-Cl-thien-2-yl	7-PhS-
384	5-Cl-thien-2-yl	7-CH_3S- 9-CH_3S-
385	5-Cl-thien-2-yl	7-CH_3O- 9-CH_3O-
386	5-Cl-thien-2-yl	7-Et-
387	5-Cl-thien-2-yl	7-iPr-
388	5-Cl-thien-2-yl	7-t-Bu-
389	5-Cl-thien-2-yl	7-CH_3O-
390	5-Cl-thien-2-yl	7-CH_3S-
391	5-Cl-thien-2-yl	7-Me
392	thien-2-yl	7-(1-azetidine) 9-CH_3-
393	thien-2-yl	7-EtS- 9-CH_3-
394	thien-2-yl	7-$CH_3S(O)$- 9-CH_3-
395	thien-2-yl	7-$CH_3S(O)_2$- 9-CH_3-

396	thien-2-yl	7-PhS- 9-CH_3-
397	thien-2-yl	7-CH_3S- 9-CH_3-
398	thien-2-yl	7-CH_3O- 9-CH_3-
399	thien-2-yl	7-CH_3- 9-CH_3-
400	thien-2-yl	7-CH_3O- 9-CH_3O-
401	thien-2-yl	7-(1-pyrazrole)
402	thien-2-yl	7-(N)-N'-methylpiperazine
403	thien-2-yl	Ph-
404	thien-2-yl	7-$CH_3C(=CH_2)$-
405	thien-2-yl	7-cyclpropyl
406	thien-2-yl	7-$(CH_3)_2NH$ -
407	thien-2-yl	7-(N)-azetidine 9-CH_3S-
408	thien-2-yl	7-(N-pyrrolidine) 9-CH_3S-
409	thien-2-yl	7-$(CH_3)_2N$- 9-CH_3S-
411	5-Cl-thien-2-yl	7-(1-pyrazrole)
412	5-Cl-thien-2-yl	7-(N)-N'-methylpiperazine
413	5-Cl-thien-2-yl	Ph-
414	5-Cl-thien-2-yl	7-$CH_3C(=CH_2)$-
415	5-Cl-thien-2-yl	7-cyclopropyl
416	5-Cl-thien-2-yl	7-$(CH_3)_2NH$ -

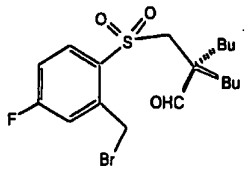
417	5-Cl-thien-2-yl	7-(N)-azetidine 9-CH_3S-
418	5-Cl-thien-2-yl	7-(N-pyrrolidine)- 9-CH_3S-
419	5-Cl-thien-2-yl	7-$(CH_3)_2N$- 9-CH_3S-
420	5-Cl-thien-2-yl	7-(1-azetidine) 9-CH_3-
421	5-Cl-thien-2-yl	7-EtS- 9-CH_3-
422	5-Cl-thien-2-yl	7-$CH_3S(O)$- 9-CH_3-
423	5-Cl-thien-2-yl	7-$CH_3S(O)_2$- 9-CH_3-
424	5-Cl-thien-2-yl	7-PhS- 9-CH_3-
425	5-Cl-thien-2-yl	7-CH_3S- 9-CH_3-
426	5-Cl-thien-2-yl	7-CH_3O- 9-CH_3-
427	5-Cl-thien-2-yl	7-CH_3- 9-CH_3-
428	5-Cl-thien-2-yl	7-CH_3O- 9-CH_3O-
429	thien-2-yl	6-CH_3O- 7-CH_3O- 8-CH_3O-
430	5-Cl-thien-2-yl	6-CH_3O- 7-CH_3O- 8-CH_3O-

Examples 232-1394

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 1. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5-positions (R^3, R^4, R^5, R^6) and in the indicated position on the benzo ring (R^7).

Example 1395

Dibutyl 4-fluorobenzene dialdehyde



Step 1: Preparation of dibutyl 4-fluoro benzene dialdehyde

To a stirred solution of 17.5 g (123 mmol) of 2,5-difluorobenzaldehyde (Aldrich) in 615 mL of DMSO at ambient temperature was added 6.2 g (135 mmol) of lithium sulfide (Aldrich). The dark red solution was stirred at 75 C for 1.5 hours, or until the starting material was completely consumed, and then 34 g (135 mmol) of dibutyl mesylate aldehyde was added at about 50 C. The reaction mixture was stirred at 75 C for three hours or until the reaction was completed. The cooled solution was poured into water and extracted

with ethyl acetate. The combined extracts were washed with water several times, dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 23.6 g (59%) of fluorobenzene dialdehyde as a yellow oil: ^1H NMR ($CDCl_3$) d 0.87 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.78 (m, 4H), 3.09 (s, 2H), 7.2-7.35 (m, 1H), 7.5-7.6 (m, 2H), 9.43 (s, 1H), 10.50 (d, J = 2.62 Hz, 1H).

Step 2: Preparation of dibutyl 4-fluorobenzyl alcohol

To a solution of 22.6 g (69.8 mmol) of the dialdehyde obtained from Step 1 in 650 mL of THF at -60 C was added 69.8 mL (69.8 mmol) of DIBAL (1M in THF) via a syringe. The reaction mixture was stirred at -40 C for 20 hours. To the cooled solution at -40 C was added sufficient amount of ethyl acetae to quench the excess of DIBAL, followed by 3 N HCl. The mixture was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 13.5 g (58%) of recovered starting material, and 8.1 g (36%) of the desired fluorobenzyl alcohol as a colorless oil: ^1H NMR ($CDCl_3$) d 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.72 (m, 4H), 1.94 (br s, 1H), 3.03 (s, 2H), 4.79 (s, 2H), 6.96 (dt, J = 8.46, 3.02 Hz, 1H), 7.20 (dd, J = 9.47, 2.82 Hz, 1H), 7.42 (dd, J = 8.67, 5.64, 1H), 9.40 (s, 1H).

Step 3: Preparation of dibutyl 4-fluorobenzyl bromide

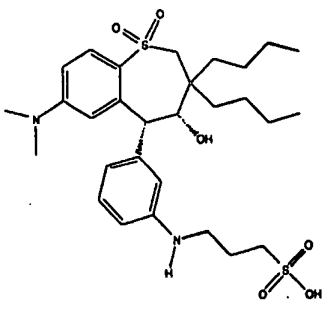
To a solution of 8.1 g (25 mmol) of benzyl alcohol obtained from Step 2 in 100 mL of DMF at -40 C was added 47 g (50 mmol) of bromotriphenyphosphonium bromide (Aldrich). The resulting solution was stirred cold for 30 min, then was allowed to warm to 0 C. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed a few times with water, dried (MgSO4), and concentrated in vacuo.

The mixture was stirred in small amount of ethyl acetate/hexane mixture (1:4 ratio) and filtered through a pad of silica gel, eluting with same solvent mixture. The combined filtrate was concentrated in vacuo to give 9.5 g (98%) of the desired product as a colorless oil: ^{1}H NMR ($CDCl_3$) d 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.55-1.78 (m, 4H), 3.11 (s, 2H), 4.67 (s, 2H), 7.02 (dt, J = 8.46, 3.02 Hz, 1H), 7.15 (dd, J = 9.47, 2.82 Hz, 1H), 7.46 (dd, J = 8.67, 5.64, 1H), 9.45 (s, 1H).

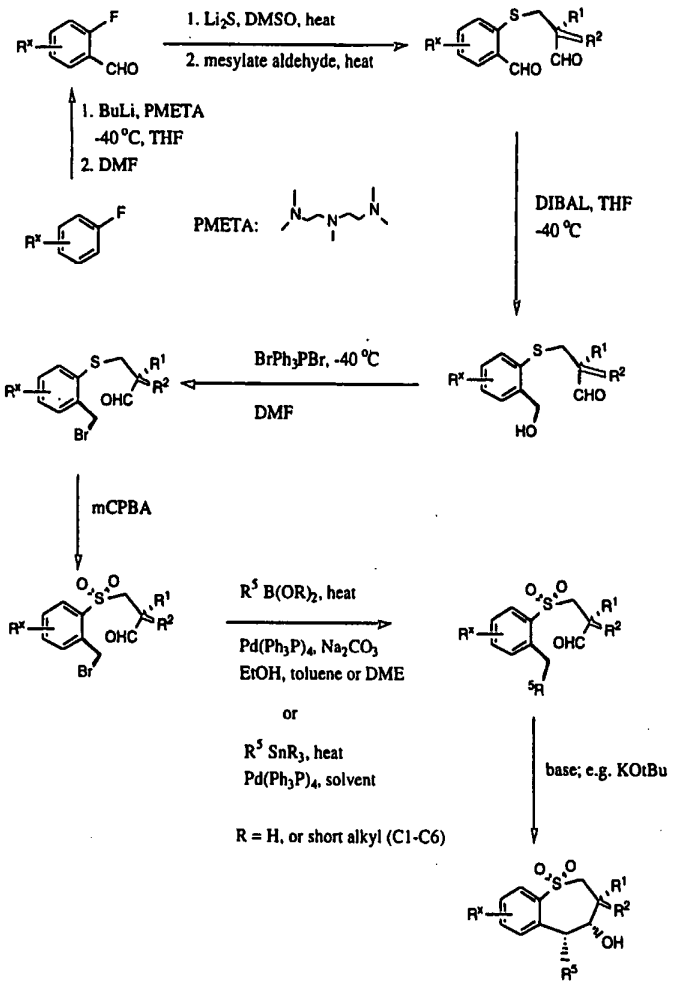
Step 4: Preparation of sulfonyl 4-fluorobenzyl bromide

To a solution of 8.5 g (25 mmol) of sulfide obtained from Step 3 in 200 mL of CH_2Cl_2 at 0 ^{0}C was added 15.9 g (60 mmol) of mCPBA (64% peracid). The resulting solution was stirred cold for 10 min, then was allowed to stirred ambient temperature for 5 hours. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed several times with saturated Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo to give 10.2 g (98%) of the desired product as a colorless oil: ^{1}H NMR ($CDCl_3$) d 0.91 (t, J = 7.05 Hz, 6H), 1.03-1.4 (m, 8H), 1.65-1.82 (m, 2H), 1.90-2.05 (m, 2H), 3.54 (s, 2H), 5.01 (s, 2H), 7.04-7.23 (m, 1H), 7.30 (dd, J = 8.87, 2.42 Hz, 1H), 8.03 (dd, J = 8.86, 5.64, 1H), 9.49 (s, 1H).

Example 1396



Generic Scheme X



Generic Scheme X: The nucleophilic substitution of an appropriately substituted 2-fluorobenzaldehyde with lithium sulfide or other nucleophilic sulfide anion in polar solvent (such as DMF, DMA, DMSO ..etc), followed by the addition of dialkyl mesylate aldehyde (**X**), provided a dialkyl benzene dialdehyde **Y**. DIBAL reduction of the dialdehyde at low temperature yielded benzyl alcohol monoaldehyde **Z**. Conversion of benzyl alcohol to benzyl bromide, followed by oxidation of sulfide to sulfone yielded the key intermediate **W**.

Preparation of N-propylsulfonic acid

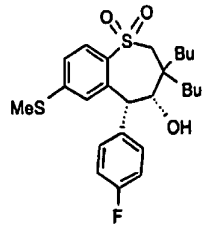
To a solution of 51 mg (111 µm) Compound X in ethanol (400 µl) was added 1,3 propane sultone (19.5 µl, 222 µm). The reaction was stirred in a sealed vial at 55 °C for 25 hr. Sample was concentrated under a nitrogen stream and purified by reversed phase chromatography using acetonitrile/water as eluent (30-45%) and afforded the desired material as an off-white solid (28.4 mg, 44%): ^{1}H NMR ($CDCL_3$) d 0.82-0.96 (m, 6H), 1.11-1.52 (m of m, 10H), 1.58-1.72 (m, 1H), 2.08-2.21 (m, 1H), 2.36-2.50 (m, 2H), 2.93 (s, 6H), 3.02-3.22 (m of m, 5H), 3.58-3.76 (m, 2H), 4.15 (s, 1H), 5.51 (s, 1H), 6.45-6.58 (m, 1H), 6.92-7.02 (m, 1H), 7.35-7.41 (m, 1H), 7.41-7.51 (m, 2H), 8.08 (d, J = 8.1 Hz, 1H), 8.12-8.25 (m, 1H); MS ES- M-H m/z 579.

Example 1397

The 7-fluoro, 9-fluoro and 7,9-difluoro analogs of benzothiepine compounds of this invention can be reacted with sulfur and nitrogen nucleophiles to give the corresponding sulfur and nitrogen substituted analogs. The following example demonstrates the

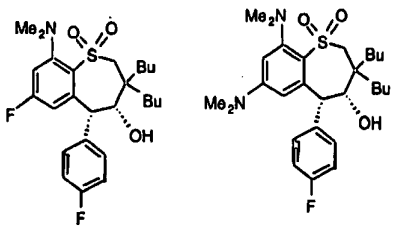
synthesis of these analogs.

3,3-Dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.



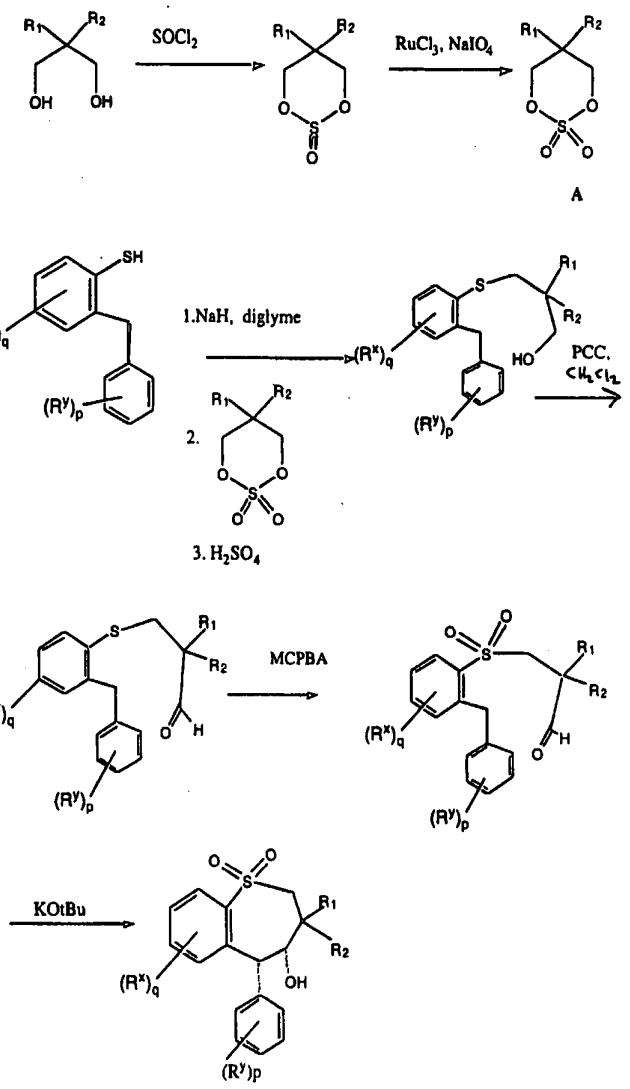
A mixture of 0.4 g 0f 3,3-dibutyl-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by previously described method, 0.12 g of sodium methanethiolate and 20 ml of DMF was stirred at 50 C for 3 days. An additional 0.1 g of sodium methanethiolate was added to the reaction mixture and the mixture was stirred for additional 20 h at 50 C then was concentrated in vacuo. The residue was triturated with water and extracte wiith ether. The ether extract was dried over $MgSO_4$ and concentrated in vacuo to 0.44 g of an oil. Purification by HPLC (10% EtOAc in hexane) gave 0.26 g of needles, mp 164-165.5 %C.

3,3-Dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide and 7,9-Bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.



A solution of 0.105 g of 3,3-dibutyl-7,9-difluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by the method described previously, in 20 ml of 2 N dimethylamine in THF was heated at 160 C in a sealed Parr reactor overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with 25 ml of water and extracted with ether. The ether extract was dried over $MgSO_4$ and concentrated in vacuo. The resdue was purified by HPLC (10% EtOAc in hexane) to give 35 mg of an earlier fraction which was identified as 3,3-dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 480 (M^+ +1), and 29 mg of a later fraction which was identified as 7,9-bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 505 (M^+ +1).

The compounds of this invention can also be synthesized using cyclic sulfate (A, below) as the reagent as shown in the following scheme. The following example describes a procedure for using the cyclic sulfate as the reagent.

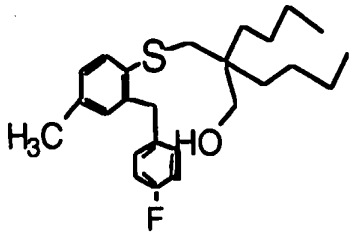


Dibutyl cyclic sulfite:

A solution of 2,2-dibutyl-1,3-propandiol (103g, 0.548 mol) and triethylamine (221g, 2.19 mol) in anhydrous methylene chloride (500 ml) and was stirred at 0 degrees C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise and within 5 min the solution turned yellow and then turned black when the addition was completed within half an hour. The reaction mixture was stirred for 3 hrs. GC showed that there was no starting material left. The mixture was washed with ice water twice then with brine twice. The organic phase was dried over magnesium sulfate and concentrated under vacuum to give the cyclic sulfite 128 g (100%) as a black oil. Mass spectrum (MS) was consistent with the product.

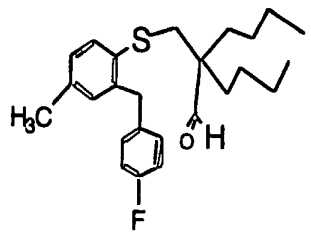
To a solution of the above compound (127.5g , 0.54 mol) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium(III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. GC showed that there was no starting material left. The mixture was extracted with 300 ml of ether and the ether extract was washed three times with brine. The organic phase was dried over magnesium sulfate and passed through celite. The filtrate was concentrated under vacuum and gave the cyclic sulfate 133 g (97.8%) as an oil. Proton, carbon NMR and MS were consistent with the product.

2-[(2-(4'-Fluorobenzyl)-4-methylphenylthio)methyl]-2-butylhexanol:



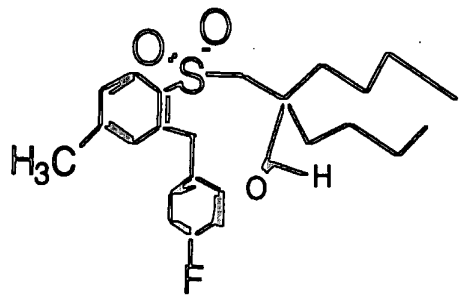
Sodium hydride (60% oil dispersion), 0.27 g (6.68 mmole), was washed with hexane and the hexane wash was decanted. To the washed sodium hydride was added 20 ml of 2-methoxyethyl ether (diglyme) and the mixture was cooled in an ice bath. A solution of 1.55 g (6.68 mmole) of 2-(4'-fluorobenzyl)-4-methylbenzenethiol in 10 ml of 2-methoxyethyl ether was added dropwise to the reaction mixture in 15 min. A mixture of 2.17 g (8.68 mmole) of the dibutyl cyclic sulfate in 10 ml of 2-methoxyethyl ether was added once and stirred for 30 min at 0 C then at room temperature for 1 hr under nitrogen. GC showed that there was no thiol left. The solvent was evaporated and triturated wth water then was extracted with ether twice. The water layer was separated, treated with 20 ml of 10% NaOH then was boiled for 30 min and cooled, acidified with 6N HCl and boiled for 10 min. The reaction mixture was cooled and extracted with ether. The organic layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under vacuum to give 2.47 g (92.5%) of an oil. Proton NMR , ^{13}C NMR and MS were consistent with the product.

2-[(2-(4'-Fluorobenzyl)-4-methylphenylthio)methyl]-2-butylhexanal:



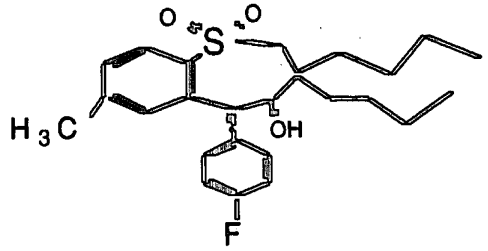
To a solution of the above product (2 g , 4.9 mmol) in 40 ml methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmol) at once. The reaction was stirred with 3 hrs and filtered through a bed of silica gel. The filtrate was concentrated under vacuum to give 1.39 g (70%) of an oil. Proton, carbon NMR and MS were consistent with the product.

2-[(2-(4'-Fluorobenzyl)-4-methylphenylsulfonyl)methyl]-2-butylhexanal



To a solution of the above product (0.44 g ,1.1 mmole) in 20 ml methylene chloride solution cooled in an ice bath under nitrogen was added 70% m-chloroperbenzoic acid (0.54 g, 2.2 mmol) at once. The reaction mixture was stirred for 18 hrs and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, dried over magnesium sulfate and concentrated under vacum to give 0.42 g (90%) of an oil. Proton, carbon NMR and MS were consistent with the product.

3,3-Dibutyl-7-methyl-5a-(4'-fluorophenyl)-6a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide:

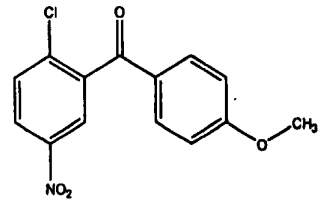


A mixture of 0.37 g (0.85 mmol) of the above product in 30 ml of anhydrous THF was stirred at 0 %C. Then potassium t-butoxide (102 mg, 0.85 mmol) was added. After 3 hrs, TLC showed that there was a product and some starting material left. The crude reaction mixture was acidified with 10% HCl and extracted with ether. The ether extract was washed successively with water and brine, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc-Hexane). The first fraction was 0.1 g of starting material as an oil and the second fraction was a white solid, 0.27 g (75%). Proton NMR and carbon NMR were consistent with the desired product. Mass spectrum (CI)

also confirmed the product, m/e 433 (M^+ 1).

Example 1398

Step 1



$C_{14}H_{10}ClNO_4$ fw=291.69

In an inert atmosphere, weigh out 68.3 gms phosphorus pentachloride (0.328mole Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Fit flask with a N_2 inlet adapter and suba seal. Remove from inert atmosphere and begin N_2 purge. Add 50mls anhydrous chlorobenzene (Aldrich 28,451-3) to the PCl_5 via syringe and begin stirring with magnetic stir bar.

Weigh out 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3). Slowly add to the chlorobenzene solution while under N_2 purge. Stir at room temperature overnight. After stirring at room temperature for ~20hrs, place in oil bath and heat at 50C for 1hr. Remove chlorobenzene by high vacuum. Wash residue with anhydrous hexane. Dry acid chloride wt=61.95gms. Store in inert and dry atmosphere.

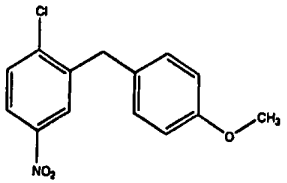
In inert atmosphere, dissolve acid chloride with 105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask.

Weigh out 45.1gms aluminum chloride (0.34 moles Aldrich 29,471-3) and place in a solid addition funnel. Fit reaction flask with addition funnel and a N_2 inlet adapter. Remove from inert atmosphere. Chill reaction solution with ice bath and begin N_2 purge. Slowly add

$AlCl_3$ to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight .

Quench reaction by pouring into a solution of 300 mls 1N HCl and ice. Stir 15 min. Extract twice with ether. Combine organic layers and extract twice with 2% NaOH, then twice with deionized H_2O. Dry with $MgSO_4$, filter and rotovap to dryness. Remove anisole by high vacuum. Crystalize product from 90% ethanol 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms. Yield 41%. Obtain NMR and mass spec (m/z=292).

Step 2



$C_{14}H_{13}ClNO_3$ fw=277.71

Dissolve 38.10gms (0.131 moles) of the benzophenone from step 1 in 250mls anhydrous methylene chloride. Place in a 3 liter flask fitted with N_2 inlet, addition funnel and stopper. Stir with magnetic stir bar. Chill solution with ice bath.

Prepare a solution of 39.32 gms trifluoromethane sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. Stir 5 minutes after addition is complete.

Prepare a solution of 22.85 gms triethyl silane (0.197mole Aldrich 23,019-7) and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. Stir 5 minutes after addition is complete.

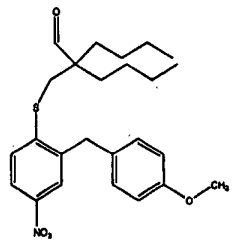
Prepare a second solution of 39.32 gms trifluoromethane sulfonic acid and 170mls anhydrous

methylene chloride.. Place in addition funnel and add dropwise to chilled solution under N_2. Stir 5 minutes after addition is complete.

Prepare a second solution of 22.85 gms triethyl silane and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2. After all additions are made allow to slowly warm to room temperature overnight. Stir under N_2 overnight.

Prepare 1300 mls saturated $NaHCO_3$ in a 4 liter beaker. Chill with ice bath. While stirring vigorously, slowly add reaction mixture. Stir at chilled temperature for 30 min. Pour into a separatory funnel and allow separation. Remove organic layer and extract aqueous layer 2 times with methylene chloride. Dry organic layers with $MgSO_4$. Crystallize from ethanol. Dry on vacuum line. Dry wt=28.8gms. Confirm by NMR and mass spec (m/z=278).

Step 3



$C_{21}H_{23}NO_4S$ fw=443.61

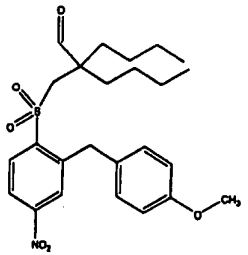
Dissolve 10.12 gms (0.036 moles) of product 2 with 200 mls anhydrous DMSO. Place in a 500 ml round bottom flask with magnetic stir bar. Fit flask with water condenser, N_2 inlet, and stopper. Add 1.84 gms Li_2S (0.040 moles Aldrich 21,324-1). Place flask in oil bath and heat at 75°C under N_2 overnight then cool to

room temperature.

Weigh out 10.59 gms dibutyl mesylate (0.040 moles). Dissolve with anhydrous DMSO and add to reaction solution. Purge well with N_2, heat overnight at 80°C.

Cool to room temperature. Prepare 500 mls of 5% acetic acid in a 2 liter beaker. While stirring, slowly add reaction mixture. Stir 30 min. Extract with ether 3 times. Combine organic layers and extract with water and sat'd NaCl. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry oil on vacuum line. Obtain pure product by column chromatography using 95% hexane and 5% ethyl acetate as the mobile phase. Dry wt=7.8 gms. Obtain NMR and mass spec (m/z=444).

Step 4

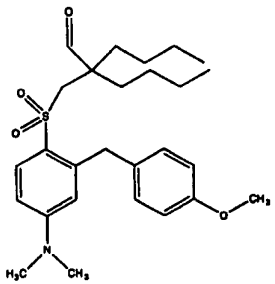


$C_{25}H_{33}NO_6S$ fw=475.61

Dissolve 9.33 gms (0.021 moles) of product 3 with 120 mls anhydrous methylene chloride. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice bath under N_2 purge. Slowly add 11.54 gms 3-chloroperbenzoic acid (0.0435 moles, Fluka 25800, ~65%). After addition is complete warm to room temperature and monitor reaction by TLC. Reaction goes

quickly to the sulphoxide intermediate but takes 8 hrs to convert to the sulphone. Chill solution over night in freezer. Filter solid from reaction, extract filtrate with 10% K_2CO_3. Extract aqueous layer twice with methylene choride. Combine organic layers and dry with $MgSO_4$. Filter and rotovap to dryness. Obtain pure product by crystallizing from ethanol or isolating by column chromatography. Obtain NMR and mass spec (m/z=476).

Step 5



$C_{27}H_{39}NO_4S$ fw=473.68

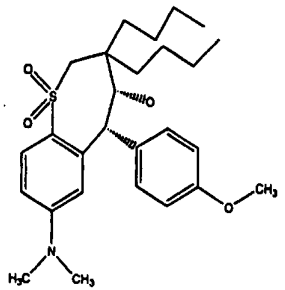
Reaction is done in a 300 ml stainless steel Parr stirred mini reactor. Place 9.68 gms (0.0204 moles) of product 4 in reactor base. Add 160 mls ethanol. For safety reasons next two compounds are added in a N_2 atmosphere glove bag. In glove bag, add 15.3 mls formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich 20,569-9). Seal reactor before removing from glove bag. Purge reactor three times with H_2. Heat to 55°C under H_2. Run reaction at 200 psig H_2, 55°C, and a stir rate of 250 rpm. Run overnight under these conditions.

Cool reactor and vent H_2. Purge with N_2. Check progress of run by TLC. Reaction is a mixture of desired product and intermediate. Filter reaction

mixture over a bed of celite washing well with ether. Rotovap and redissolve with ether. Extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line.

Charge reactor again with same amounts, seal reactor and run overnight under same conditions. After second run all of the material has been converted to the desired product. Cool and vent H_2 pressure. Purge with N_2. Filter over a bed of celite, washing well with ether. Rotovap to dryness. Dissolve with ether and extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line. Obtain NMR and mass spec (m/z=474).

Step 6

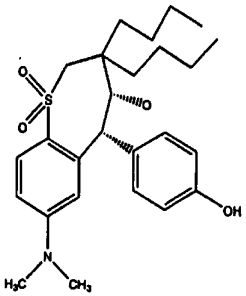


$C_{27}H_{39}NO_4S$ fw=473.68

Dissolve 8.97 gms (0.0189 mole) of product 5 with 135 mls anhydrous THF. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice/salt bath under N_2 purge. Slowly add 2.55 gms potassium t-butoxide (0.227 mole Aldrich 15,667-1). After addition is complete, continue to stir at -10°C monitoring by TLC. Once reaction is complete, quench by adding 135 mls 10% HCl stirring 10 min. Extract three times with

ether. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Crystallize from ether. Obtain NMR and mass spec (m/z=474).

Step 7

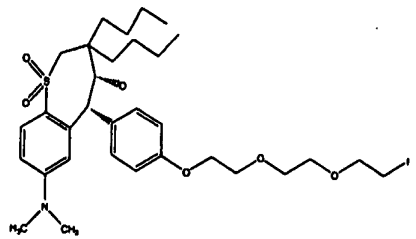


$C_{26}H_{37}NO_4S$ fw=459.65

Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N_2 purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

Chill solution with ice bath. Quench with 100 mls 10% K_2CO_3 while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl, once H_2O, and once with saturated NaCl solution. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec (m/z=460).

Step 8



$C_{32}H_{48}NO_6SI$ fw=701.71

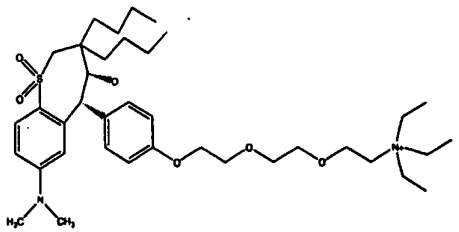
Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 60% disp. in mineral oil) in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill NaH with ice bath and begin N_2 purge.

Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 mls anhydrous DMF. Add to the cold NaH. Stir at cold temperature for 30 min. Add 1.33 gms K_2CO_3 (9.57 mmoles Fisher P-208).

Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane (43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous DMF. Add to cold reaction mixture. Warm to room temperature then heat to 40°C overnight under N_2.

Cleanup by diluting with ether and extracting sequentially with 5% NaOH, H_2O, and saturated NaCl. Dry organic layer with $MgSO_4$, filter and dry. Obtain pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and mass spec (m/z=702).

Step 9



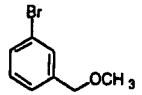
$C_{38}H_{63}N_2O_6SI$ fw=802.90

Dissolve 1.0 gms (1.43 mmoles) of product 8 with 10 mls anhydrous acetonitrile. Place in a 3 ounce Fischer-Porter pressure reaction vessel with magnetic stir bar. Add 2.9 gms triethyl amine (28.6 mmoles Aldrich 23,962-3) dissolved in 10 mls anhydrous acetonitrile. Purge well with N_2 then close system. Heat at 45°C. Monitor reaction by TLC. Reaction is usually complete in 48 hrs.

Perform cleanup by removing acetonitrile under vacuum. Redissolve with anhydrous chloroform and precipitate quaternary ammonium salt with ether. Repeat several times. Dry to obtain crystalline product. Obtain NMR and mass spec (m/z=675).

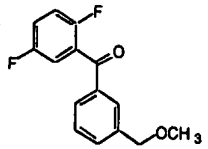
Example 1399

Step 1. Preparation of **1**



To a solution of 144 g of KOH (2560 mmol) in 1.1 L of DMSO was added 120 g of 2-bromobenzyl alcohol (641 mmol) slowly via addition funnel. Then was added 182 g of methyliodide (80 mL, 1282 mmol) via addition funnel. Stirred at ambient temperature for fifteen minutes. Poured reaction contents into 1.0 L of water and extracted three times with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purified by silica-gel chromatography through a 200 mL plug using hexanes (100%) as elutant yielded 103.2 g (80%) of **1** as a clear colorless liquid. ^1H NMR ($CDCl_3$) d 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, 2H), 7.12 (d, J = 7.45, 1H), 7.50 (s, 1H).

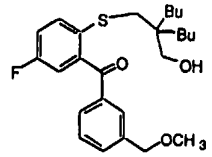
Step 2. Preparation of **2**



To a cooled (-78 °C) solution of 95 g (472 mmol) of **1** in 1.5 L THF was added 240 mL of 2.5 M n-butyl lithium (576 mmol). The mixture was stirred for one hour, and then to it was added 180 g of zinc iodide (566 mmol) dissolved in 500 ml THF. The mixture was stirred thirty minutes, allowed to warm to 5 C, cooled to -10 °C and to it was added 6 g of $Pd(PPh_3)_4$ (5.2 mmol) and 125 g 2,5-difluorobenzoyl chloride (708 mmol). The mixture was stirred at ambient temperature for 18

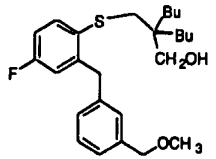
hoursand then cooled to 10 °C, quenched with water, partitioned between ethyl acetate and water, and washed organic layer with 1N HCL and with 1N NaOH. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 5% ethyl acetate/hexanes as elutant gave 53.6 g (43 %) of **2** as an orange oil. ^1H NMR ($CDCl_3$) d 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H).

Step 3. Preparation of **3**



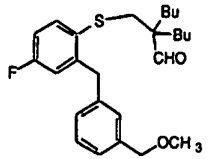
A solution of 53 g (202.3 mmol) of **2** and 11.2 g Li2S (242.8 mmol) in 250 mL DMF was heated to 100 °C for 18 hours. The reaction was cooled (0 °C) and 60.7 g of X (the cyclic sulfate compound of example 1397) (242.8 mmol) in 50 mL DMF was added. Stirred at ambient temperature for 18 hours then condensed in vacuo. Added 1 L water to organic residue and extracted twice with diethyl ether. Aqueous layer acidified (pH 1) and refluxed 2 days. Cooled to ambient temperature and extracted with methylene chloride, dried organic layer over $MgSO_4$ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate / hexanes as elutant gave 42.9 g (48 %) of **3** as a yellow oil. ^1H NMR ($CDCl_3$) d 0.86 (t, J = 7.25 Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 (s, 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, J = 8.26 Hz and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and 2.82 Hz, 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, 2H), 7.69 (d, J = 7.85 Hz, 1H), 7.74 (s, 1H).

Step 4. Preparation of 4



To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of 3 in 200 mL of methylene chloride was added 21.6 g trifluoromethane sulfonic acid (12.8 mL, 144 mmol) followed by the addition of 22.4 g triethyl silane (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, quenched with water and warmed to ambient temperature. Partitioned between methylene chloride and water, dried the organic layer over $MgSO_4$ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate/ hexanes as elutant gave 24.2 g (60%)of 4 as a oil. ^1H NMR ($CDCl_3$) d 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), 1.46 (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (s, 2H), 4.42 (s, 2H), 6.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 7.09 (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 - 7.32 (m, 2H), 7.42 (m, 1H).

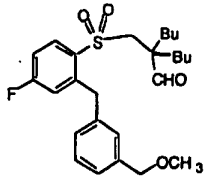
Step 5. Preparation of 5



To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of 4 in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water

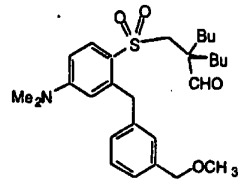
and extracted three times with ethyl acetate. Washed organics with 5% HCl (300 mL) and then with brine (300 mL), dired organics over $MgSO_4$ and condensed in vacuo to give 23.1 g (96 %) of 5 as a light brown oil. ^1H NMR ($CDCl_3$) d 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, J = 9.66 Hz and 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, J = 7.46 Hz, 1H), 7.14 (s, 1H), 7.19 (d, J = 7.65 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

Step 6. Preparation of 6



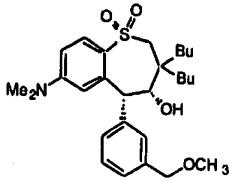
To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of 5 in 200 mL methylene chloride was added 28.6 g meta cholorperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na_2SO_3, partitioned between water and methylene chloride. Dried organic layer over $MgSO_4$ and condensed in vacuo to give 24.5 g (98%) of 6 as a light yellow oil. ^1H NMR ($CDCl_3$) d 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (s, 2H), 3.39 (s, 3H), 4.44 (s, 2H), 4.50 (s, 2H), 6.93 (d, J = 9.07 Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (s, 1H), 9.38 (s, 1H).

Step 7. Preparartion of 7



To a solution of 24.5 g (52.9 mmol) of **6** in 20 mL of THF contained in a stainless steel reaction vessel was added 100 mL of a 2.0 M solution of dimethyl amine and 20 mL of neat dimethyl amine. The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 15 % ethyl acetate/hexanes gave 21.8 g (84 %) of **7** as a clear colorless oil. ^{1}H NMR ($CDCl_3$) d 0.85 (t, J = 7.25 Hz, 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 - 1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, 2H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (s, 1H), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 1H), 9.36 (s, 1H).

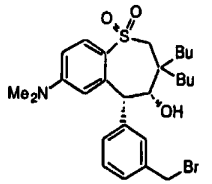
Step 8. Preparation of **8**



A solution of 21.8 g (44.8 mmol) of **7** in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirred for 30 minutes, then

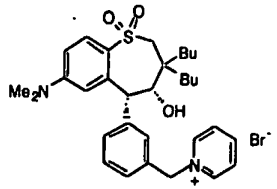
quenched with 50 mL of saturated ammonium chloride. The organic layer was partitioned between ethyl acetate and water, dried over MgSO4 and concentrated in vacuo. Purification by recrystalization from ~10% ethyl acetate/hexanes gave 15.1 g of **8** as a white solid. The mother liquor was purified by silica gel chromatography (Waters Prep-500) using 30% ethyl acetate/hexanes as the elutant to give 3.0 g of **8** as a white solid. MS (FABLi$^+$) m/e 494.6. HRMS (EI$^+$) calculated for M+H 487.2756. Found 487.2746.

Step 9. Preparation of **9**



A solution of 2.0 g (4.1 mmol) of **8** in 20 mL of methylene chloride was cooled to -60 °C. 4.1 mL of a 1M solution of boron tribromide was added. Stirred at ambient temperature for thirty minutes. Cooled reaction to ~10 °C and quenched with 50 mL of water. The organic layer was partitioned between methylene chloride and water, dried over $MgSO_4$ and concentrated in vacuo. Purification by recrystalization from 50% ethyl acetate/methylene chloride gave 1.95 g (89%) of **9** as a white solid. MS (FABH$^+$) m/e 537. HRMS (FAB) calculated for M 536.1834. Found 536.1822.

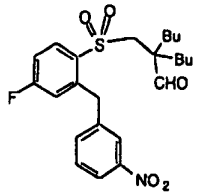
Step 10. Preparation of **10**



A solution of 1.09 g (2.0 mmol) of **9** and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacuo. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of **10** as an off white solid. MS (FAB$^+$) m/e 535.5.

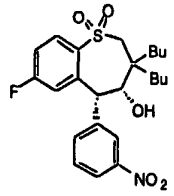
Example 1398

Step 1. Preparation of **2**



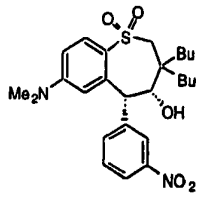
To a solution of 6.0 g of dibutyl 4-fluorobenzene dialdehyde of Example 1395 (14.3 mmol) in 72 mL of toluene and 54 mL of ethanol was added 4.7 g 3-nitrobenzeneboronic acid (28.6 mmol), 0.8 g of tetrakis (triphenylphosphine) palladium(0) (0.7 mmol) and 45 mL of a 2 M solution of sodium carbonate in water. This heterogeneous mixture was refluxed for three hours, then cooled to ambient temperature and partitioned between ethyl acetate and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-2000) using ethyl acetate/hexanes (25/75) gave 4.8 g (73%) of the title compound as a yellow solid. ^1H NMR ($CDCl_3$) d 0.88 (t, J = 7.45 Hz, 6H), 0.99-1.38 (m, 8H), 1.62-1.75 (m, 2H), 1.85-2.00 (m, 2H), 3.20 (s, 2H), 4.59 (s, 2H), 6.93 (dd, J = 10.5 and 2.4 Hz, 1H), 7.15 (dt, J = 8.4 and 2.85 Hz, 1H), 7.46-7.59 (m, 2H), 8.05-8.16 (m, 3H), 9.40 (s, 1H).

Step 3. Preparation of 3



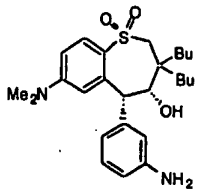
A solution of 4.8 g (10.4 mmol) of 2 in 500 mL THF was cooled to 0 °C in an ice bath. 20 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirring was continued for 30 minutes, then the reaction was quenched with 100 mL of saturated ammonium chloride. The mixture was partitioned between ethyl acetate and water; the organic layer was washed with brine, then dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel chromatography through a 100 ml plug using CH_2Cl_2 as eluent yielded 4.3 g (90%) of 3 as a pale yellow foam. ^1H NMR ($CDCl_3$) d 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 (q_{AB}, J_{AB} = 15.0 Hz, ΔV = 33.2 Hz, 2H), 4.17 (d, J = 6.0 Hz, 1H), 5.67 (s, 1H), 6.34 (dd, J=9.6 and 3.0 Hz, 1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 9.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). MS($FABH^+$) m/e (relative intensity) 464.5 (100), 446.6 (65). HRMS calculated for M+H 464.1907. Found 464.1905.

Step 4. Preparation of 4



To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of 3 in 30 ml THF contained in a stainless steel reaction vessel was added 8.2 g dimethyl amine (182 mmol). The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-2000) using an ethyl acetate/hexanes gradient (10-40% ethyl acetate) gave 4.0 g (88%) of 4 as a yellow solid. ^1H NMR ($CDCl_3$) d 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.0 Hz, DV= 45.6 Hz, 2H), 4.90 (d, J = 9.0 Hz, 1H), 5.65 (s, 1H), 5.75 (d, J = 2.1 Hz, 1H), 6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 8.20 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (s, 1H). MS($FABH^+$) m/e (relative intensity) 489.6 (100), 471.5 (25). HRMS calculated for M+H 489.2423. Found 489.2456.

Step 5. Preparation of 5

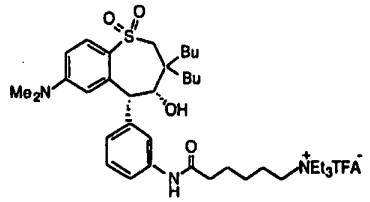


To a suspension of 1.0 g (2.1 mmol) of 4 in 100 ml ethanol in a stainless steel Parr reactor was added 1 g 10% palladium on carbon. The reaction vessel was sealed, purged twice with H_2, then charged with H_2 (100 psi) and heated to 45 °C for six hours. The reaction vessel was cooled to ambient temperature and the contents filtered to remove the catalyst. The filtrate was concentrated in vacuo to give 0.9 g (96%) of 5. ^{1}H NMR ($CDCl_3$) d 0.80-0.98 (m, 6H), 1.00-1.52 (m, 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 (s, 2H), 4.14 (s, 1H), 5.43 (s, 1H), 6.09 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, J = 7.8 and 1.8 Hz, 1H), 6.83 (s, 1H), 6.93 (d, J = 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H). MS(FABH$^+$) m/e (relative intensity) 459.7 (100). HRMS calculated for M+H 459.2681. Found 459.2670.

Step 6. Preparation of 6

To a solution of 914 mg (2.0 mmol) of 5 in 50 ml THF was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride. Next was added 4 g (39.6 mmol) TEA. The reaction was stirred 10 minutes, then partitioned between ethyl acetate and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel chromatography through a 70 ml MPLC column using a gradient of ethyl acetate(20-50%) in hexane as eluent yielded 0.9 g (73%) of 6 as a pale yellow oil. ^{1}H NMR ($CDCl_3$) d 0.84-0.95 (m, 6H), 1.02-1.53 (m, 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 4.10 (s, 1H), 5.51 (s, 1H), 5.95 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.3 and 2.7 Hz, 1H), 7.28 (s, 1H), 7.32-7.41 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H).

Step 7. Preparation of 7

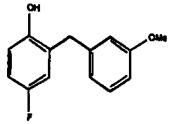


To a solution of 0.9 g (1.45 mmol) of 6 in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Purification by reverse-phase silica gel chromatography (Waters Delta Prep 3000) using an acetonitrile /water

gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of 7 as a white foam. ^{1}H NMR ($CDCl_3$) d 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.6 Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J = 1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed 642.4343.

Example 1400

Step 1

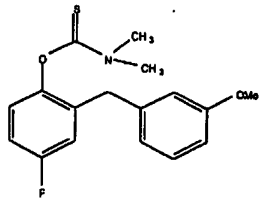


$C_{14}H_{13}O_2F$ fw=232.25

A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N_2 gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N_2. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H_2O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium

hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aq. KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ^{1}H NMR and MS [$(M + H)^+$ = 233] confirmed desired structure.

Step 2

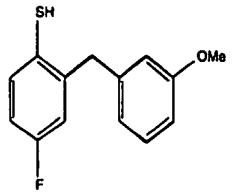


$C_{17}H_{18}NO_2FS$ fw=319.39

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo to give

the product (605.3g, 97% yield). ^{1}H NMR and MS [(M+H)$^+$ = 320] confirm desired structure.

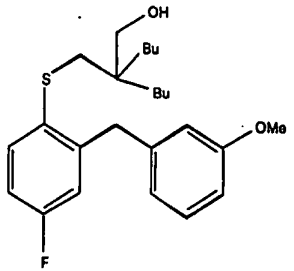
Step 3



$C_{14}H_{13}OFS$ fw=248.32

A 12-liter, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temparature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temparature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H_2O. The aqueous extracts were combined, acidified with concentrated HCl, and extracted with ethyl ether. The ether extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ^{1}H NMR confirmed desired structure.

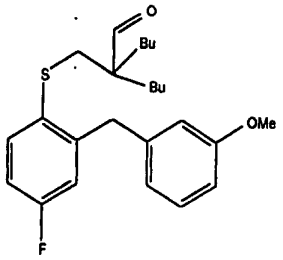
Step 4



$C_{25}H_{35}O_2FS$ fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temparature, 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H_2O. The aqueous solution was washed with ethyl ether, and concentrated H_2SO_4 was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried ($MgSO_4$), filtered, and conc'd *in vacuo* to give an amber oil (143.94g/85% yield). ^{1}H NMR and MS [(M + H)$^+$ = 419] confirm the desired structure.

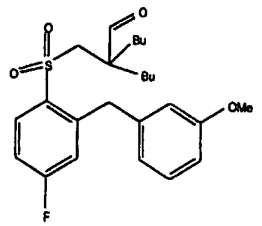
Step 5



$C_{25}H_{33}O_2FS$ fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2. The corresponding alcohol (143.94g/343.8mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS [$(M + H)^+$ = 417] confirm the desired structure.

Step 6

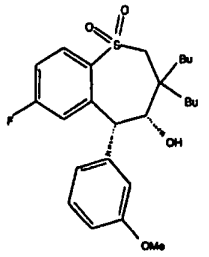


$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was

purged with N_2. The corresponding sulfide (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K_2CO_3. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ^1H NMR confirmed the desired structure.

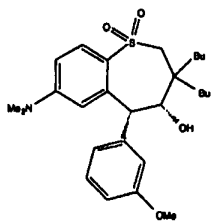
Step 7



$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 C. Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by recryst. from 80/20 hexane/ethyl acetate to give a white solid (32.18 g). The mother liquor was concentrated in vacuo and recrystelized from 95/5 toluene/ethyl acetate to give a white solid (33.60g/ combined yield: 71%). ^1H NMR confirmed the desired product.

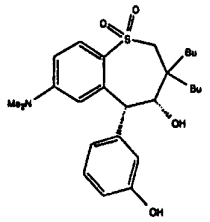
Step 8



$C_{27}H_{39}O_4NS$ fw=473.67

A Fisher porter bottle was fitted with N_2 line and magnetic stirrer. The system was purged with N_2. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a CO_2/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H_2O, saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a white solid (28.5g/96% yield). ^1H NMR confirmed the desired structure.

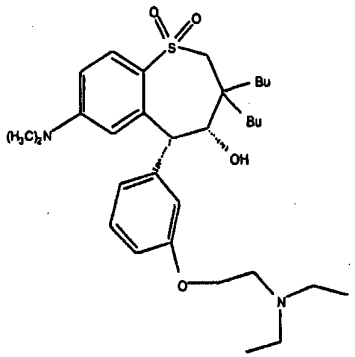
Step 9



$C_{26}H_{37}O_4NS$ fw=459.64

A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2. The corresponding methoxy-compound (6.62g/14.0mmol) and $CHCl_3$ (150 mL) were added. The reaction mixture was cooled to -78 C, and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature After 4 h, the reaction mixture was cooled to 0 C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The $CHCl_3$ and ether extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

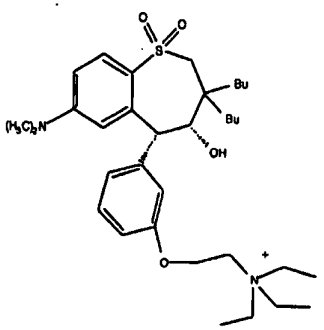
Step 10



In a 250 ml single neck round bottom Flask with stir bar place 2- diethylamineoethyl chloride hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 mmol,4.12g), 34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg , 2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product(previous step) 1.1 g (2.4 mmilomoles in 5 ml DMF and the ether solution prepared above. Heat to 40C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms).The product may be further purified by chromatography (SiO2 99% ethyl acetate/1% NH4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec , and H1 NMR)

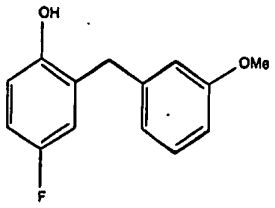
Step 11



The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was placed in 5 ml acetonitrile in a fischer-porter bottle and heated to 45 C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9 , H NMR).

Example 1401

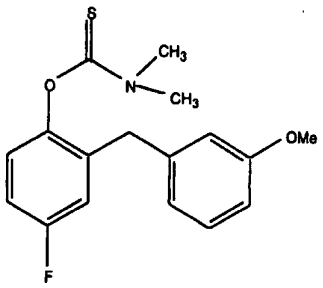
Step 1



$C_{14}H_{13}O_2F$ fw=232.25

A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N_2 gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N_2. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H_2O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aqueous KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ^1H NMR and MS [$(M + H)^+$ = 233] confirmed desired structure.

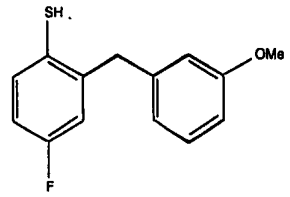
Step 2



$C_{17}H_{18}NO_2FS$ fw=319.39

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ^1H NMR and MS [$(M+H)^+$ = 320] confirm desired structure.

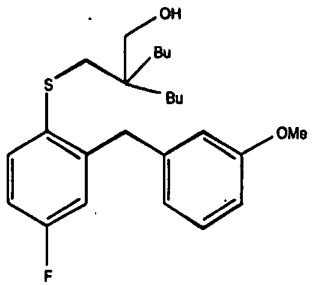
Step 3



$C_{14}H_{13}OFS$ fw=248.32

A 12-liter, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H_2O. The aqueous extracts were combined, acidified with conc. HCl, and extracted with ethyl ether. The ether extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ^1H NMR confirmed desired structure.

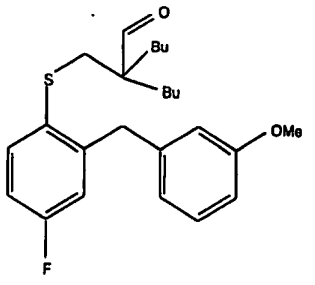
Step 4



$C_{25}H_{35}O_2FS$ fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H_2O. The aqueous solution was washed with ethyl ether, and conc. H_2SO_4 was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give an amber oil (143.94g/85% yield). ^1H NMR and MS [$(M + H)^+$ = 419] confirm the desired structure.

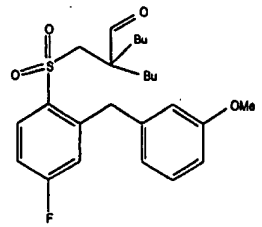
Step 5



$C_{25}H_{33}O_2FS$ fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2. The corresponding alcohol (143.94 g/343.8 mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS [$(M + H)^+$ = 417] confirm the desired structure.

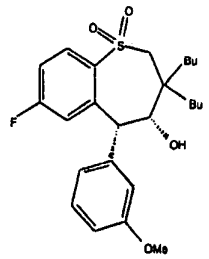
Step 6



$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2. The corresponding sulfide (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K_2CO_3. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ^1H NMR confirmed the desired structure.

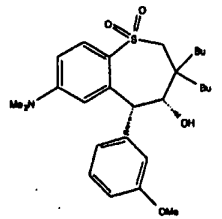
Step 7



$C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 C. Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by recrystallized from 80/20 hexane/ethyl acetate to give a white solid (32.18g). The mother liquor was concentrated in vacuo and recrystallized from 95/5 toluene/ethyl acetate to give a white solid (33.60g, combined yield: 71%). ^1H NMR confirmed the desired product.

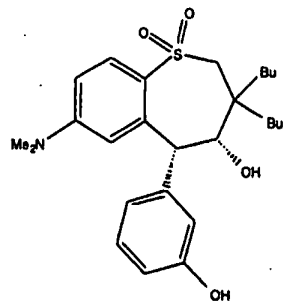
Step 8



$C_{27}H_{39}O_4NS$ fw=473.67

A Fisher porter bottle was fitted with N_2 line and magnetic stirrer. The system was purged with N_2. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a CO_2/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H_2O, saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a white solid (28.5g/96% yield). ^1H NMR confirmed the desired structure.

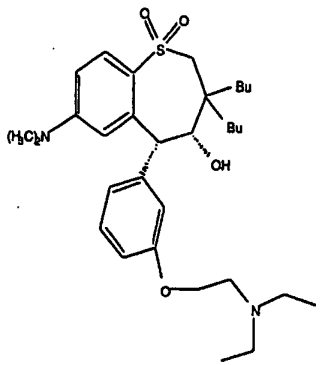
Step 9



$C_{26}H_{37}O_4NS$ fw=459.64

A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2. The corresponding methoxy-compound (6.62g/14.0mmol) and $CHCl_3$ (150 mL) were added. The reaction mixture was cooled to -78 C, and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature After 4 h, the reaction mixture was cooled to 0 C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The $CHCl_3$ and ether extracts were combined, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

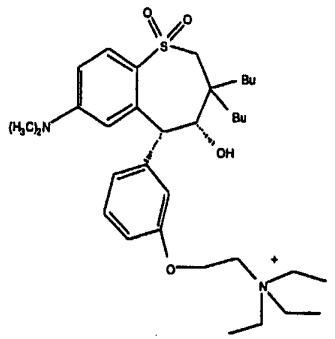
Step 10



In a 250 ml single neck round bottom flask with stir bar place 2- diethylamineoethyl chloride hydochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N KOH (aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product (previous step) 1.1 g (2.4 mmol in 5 ml DMF and the ether solution prepared above. Heat to 40C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over Magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (silica 99% ethyl acetate/1% NH4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec , and H1 NMR)

Step 11



The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and iodoethane (1.6 gms (10.02 mmilimoles)was place in 5 ml acetonitrile in a Fischer-Porter bottle and heated to 45 C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9, ^{1}H NMR).

BIOLOGICAL ASSAYS

The utility of the compounds of the present invention is shown by the following assays. These assays are performed *in vitro* and in animal models essentially using a procedure recognized to show the utility of the present invention.

In Vitro Assay of compounds that inhibit IBAT-modiated uptake of [^{14}C]-Taurocholate (TC) in H14 Cells

Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded at 60,000

cells/well in 96 well Top-Count tissue culture plates for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours.

On the day of assay, the cell monolayer is gently washed once with 100 ml assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose + 0.2% (w/v) fatty acid free bovine serum albumin- (FAF)BSA). To each well 50 ml of a two-fold concentrate of test compound in assay buffer is added along with 50 ml of 6 mM [^{14}C]-taurocholate in assay buffer (final concentration of 3 mM [^{14}C]-taurocholate). The cell culture plates are incubated 2 hours at 37° C prior to gently washing each well twice with 100 ml 4° C Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed once with 100 ml 4° C PBS without (FAF)BSA. To each 200 ml of liquid scintillation counting fluid is added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

In Vitro Assay of compounds that inhibit uptake of [^{14}C]-Alanine

The alanine uptake assay is performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

In Vivo Assay of compounds that inhibit Rat Ileal uptake of [^{14}C]-Taurocholate into Bile

(See"Metabolism of 3a,7b-dihydroxy-7a-methyl-5b-cholanoic acid and 3a,7b-dihydroxy-7a-methyl-5b-cholanoic acid in hamsters" in Biochimica et Biophysica Acta 833 (1985) 196-202 by Une et al.)

Male wistar rats (200-300 g) are anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (1/8" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum. A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum). 20 ml of warm Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). The proximal cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 min with warm PBS at 0.25 ml/min. Temperature of the gut segment is monitored continuously. At the start of the experiment, 2.0 ml of control sample ([^{14}C]-taurocholate @ 0.05 mi/ml with 5 mM cold taurocholate) is loaded into the gut segment with a 3 ml syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 ml/min for 21 min. Bile samples fractions are collected every 3 minute for the first 27 minutes of the procedure. After the 21 min of sample infusion, the ileal loop is washed out with 20 ml of warm PBS

(using a 30 ml syringe), and then the loop is washed out for 21 min with warm PBS at 0.25 ml/min. A second perfusion is initiated as described above but this with test compound being administered as well (21 min administration followed by 21 min of wash out) and bile sampled every 3 min for the first 27 min. If necessary, a third perfusion is performed as above that typically contains the control sample.

Measurement of Hepatic Cholesterol Concentration (HEPATIC CHOL)

Liver tissue was weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant was separated and dried under nitrogen. The residue was dissolved in isopropanol and the cholesterol content was measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., *et al.* (1974) *Clin. Chem.* **20**, 470.

Measurement of Hepatic HMG CoA-Reductase Activity (HMG COA)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for HMG CoA reductase activity by incubating for 60 minutes at 37° C in the presence of ^{14}C-HMG-CoA (Dupont-NEN). The reaction was stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant was separated, by thin-layer chromatography, and the spot corresponding to the enzyme product was scraped off the plate, extracted and radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) *J. Lipid Res.* **31**, 2159).

Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)

Total serum cholesterol (SER.CHOL) was measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) was assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) were assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations were calculated as the difference between total and HDL cholesterol.

Measurement of Hepatic Cholesterol 7-a-Hydroxylase Activity (7a-OHase)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for cholesterol 7-a-hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent was evaporated and the residue was dissolved in acetonitrile/ methanol. The enzymatic product was separated by injecting an aliquot of the extract onto a C_{18} reversed phase HPLC column and quantitating the eluted material using UV detection at 240nm. (Reference: Horton, J. D., *et al.* (1994) *J. Clin. Invest.* **93**, 2084).

Measurement of Fecal Bile Acid Concentration (FBA)

Total fecal output from individually housed hamsters was collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram was weighed out and extracted

into an organic solvent (butanol/water). Following separation and drying, the residue was dissolved in methanol and the amount of bile acid present was measured enzymatically using the 3a-hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., *et al.* (1981) *Clin. Chem.* **27**, 1352).

[^{3}H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

Rabbit Ileal brush border membranes were prepared from frozen ileal mucosa by the calcium precipitation method describe by Malathi *et al.* (Reference: (1979) *Biochimica Biophysica Acta*, **554**, 259). The method for measuring taurocholate was essentially as described by Kramer *et al.* (Reference: (1992) *Biochimica Biophysica Acta*, **1111**, 93) except the assay volume was 200 µl instead of 100 µl. Briefly, at room temperature a 190 µl solution containing 2µM [^{3}H]-taurocholate(0.75 µCi), 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was incubated for 5 sec with 10 µl of brush border membrane vesicles (60-120 µg protein). The incubation was initiated by the addition of the BBMV while vortexing and the reaction was stopped by the addition of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 µm pore) and an additional 5 ml wash with stop buffer.

Acyl-CoA:cholesterol Acyl Transferase (ACAT)

Hamster liver and rat intestinal microsomes were prepared from tissue as described previously (Reference: (1980) *J. Biol. Chem.* **255**, 9098) and used as a source of ACAT enzyme. The assay consisted of a 2.0 ml incubation containing 24 µM Oleoyl-CoA (0.05 µCi) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 buffer containing 0.25 % BSA and 200 µg of microsomal

protein. The assay was initiated by the addition of oleoyl-CoA. The reaction went for 5 min at 37° C and was terminated by the addition of 8.0 ml of chloroform/methanol (2:1). To the extraction was added 125 µg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction were separated by centrifugation after thorough vortexing. The chloroform phase was taken to dryness and then spotted on a silica gel 60 TLC plate and developed in hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard instaimager.

Data from each of the noted compounds in the assays described above is as set forth in TABLES 5, 6, 7, and 8 as follows:

TABLE 5

COMPOUND	IC50 uM*	In vitro % Inhibition of TC Uptake @ 100 uM #	% Inhibition of Alanine Uptake @ 100 uM #	% of Control Transport of TC in Rat Ileum @ 0.1mM #
Benzothiazepine=	2		0	45.4 +/- 0.7
12		25		
3		0		
4a		3		
5a		34		
5b	40		0	72.9 ± 5.4 @ 0.5 mM
4b		9		
18		6		
14b		18		
14a		13		
13		23		
15	60			
19a		0		
19b		15		
8a		41		
Mixture of 8a and 8b		69		
Mixture of 9a and 9b	6			
6a	5			

6b		85		
9a	5		0% @ 25 mM	53.7 +/- 3.9
Mixture of 6a and 20	13			
Mixture of 6d and 10a	0.8		14% @ 25 mM	
21a		37		
21c		52		
21b		45		
6c	2		58.5	68.8 +/- 5.7 at 0.4 mM
6d	0.6		77.7	16.1 +/- 1.1 @ 0.5 mM 30.2 +/- 0.9 @ 0.15 mM
17		10		
7	50		49.3	
10a	7		77.6	62.4 =/- 2.5 @ 0.2 mM
10b	15		68.6	
25	0.1		4% @ 10 mM	26.0 +/- 3.3
26	2		31% @ 25 mM	87.9 +/- 1.5
27	5		7% @ 20 mM	
28	8		31% @ 20mM	
29		88 @ 50 mM		
30		96 @ 50 mM		
31		41 @ 50 mM		
37	3		0% @ 5 mM	

38	0.3		11% @ 5mM	20.6 +/- 5.7
40		49 @ 50 mM		
41	2		0% @ 20 mM	
42	1.5			
43	1.5		16% @ 25 mM	
48	2		22% @ 20 mM	
49	0.15		21% @ 200 mM	21.2 +/- 2.7
57		51 @ 50 mM		
58		20 @ 50 mM		
59	70			
60	9		59	
61	30		175	
62	10			
63		90 @ 6 mM		
64		100 @ 6 mM		

* In vitro Taurocholate Cell Uptake

Unless otherwise noted

= Comparative Example is Example No. 1 in WO 93/16055

TABLE 6

Compound	TC-uptake (H14 cells) IC(50)	TC-uptake Ileal Loop EC(50)	TC-uptake (BBMV) IC(50)	ACAT (liver) IC(50)	ACAT intestine IC(50)
COMP. EXAMPLE	1 mM	74 mM	3 mM	20 mM	20 mM
6d	0.6 mM	31 mM	1.5 mM	25 mM	20 mM
* 38	0.3 mM	12 mM	2 mM	15 mM	N.D.
49	0.1 mM	12 mM	N.D.	6 mM	N.D.
25	0.1 mM	20 mM	0.8 mM	8 mM	8 mM

Comparative Example is Example No. 1 in WO 93/16055

TABLE 7
EFFICACY OF COMPOUND NO. 25 IN CHOLESTEROL-FED HAMSTERS

PARAMETER	CONTROL	4% CHOLESTYRAMINE	0.2% CPD. NO. 25
WEIGHT (G)	(mean ± SEM, *p<0.05, A-Student's t, B-Dunnett's)		
day 1	117(2)	114(6)	117(5)
day 14	127(3)	127(3)	132(4)
LIVER WEIGHT (G)	4.9(0.4)	4.9(0.4)	5.8(0.2)
SER.CHOL(mg%)	126(2)*A,B	119(4)*A,B	126(2)*A,B
HDL-CHOL(mg%)	76(1)*A,B	76(3)*A	76(1)*A,B
VLDL + LDL			
TGI(mg%)			

HEPATIC CHOL(mg/g)	).	,B	50(3)
HMG COA (pm/mg/min.)	89(4)	42(3)*A	175(11)
	54(7)	190(15)	1.9(0.1)
7a-OHase (pm/mg/min.)	203(3	1.9(0.1	*A,B
24 HR. FECAL Wt (G)	2)	)*A,B	312.9(37.5)*A
FBA (mM/24H/100g)	2.5(0	448.8(2	,B
	.3)	1.6)*A,B	
	15.8(		291.0(6.
	7.6)	357.2(2	0)*A
		8.3)*A,B	2.4(0.04
	235.3(25.1	2.7(0.1	)
	)	)*A,B	11.9(0.5
	2.3(0	12.3(1.	)*A,B
	.1)	5)*A,B	
	6.2(0		
	.8)		

TABLE 8
EFFICACY OF COMPOUND NO. 25 IN RAT ALZET MINIPUMP MODEL

PARAMETER	CONTROL	20 MPL/DAY CPD. NO. 25
WEIGHT (G)	(mean ± SEM, *p<0.05, A-Student's t, B-Dunnett's)	
day 1	307 (4)	307 (3)
day 8	330 (4)	310 (4)*A,B
LIVER WEIGHT (G)	15.5 (0.6)	14.6 (0.4)
SER.CHOL(mg%)	85 (3)	84 (3)
HEPATIC CHOL(mg/g)	21 (0.03)	2.0 (0.03)
HMG COA pm/mg/min	75.1 (6.4)	318.0 (40.7)*A,B
7a-OHase (pm/mg/min)	281.9 (13.9)	
24 HR. FECAL WT (G)	5.8 (0.1)	535.2 (35.7)*A,B
FBA (mM/24H/100g)	17.9 (0.9)	5.7 (0.4)
		39.1 (4.5)*A,B

Additional taurocholate uptake tests were conducted in the following compounds listed in Table 9.

TABLE 9

Biological Assay Data for Some Compounds of the Present Invention

Compound Number	Human TC IC_{50} (μM)	Alanine Uptake Percent Inhibition @ μM
101		0 @ 1.0
102	0.083	
103		13 @ 0.25
104	0.0056	
105	0.6	
106	0.8	
107		14.0 @ 0.063
108	0.3	
109		2.0 @ 0.063
110	0.09	
111	2.5	
112	3.0	
113	0.1	
114	0.19	
115	8.0	
116	0.3	
117		12.0 @ 0.625
118	0.4	
119	1.3	
120		34.0 @ 5.0
121	0.068	
122	1.07	
123	1.67	
124		14.0 @ 6.25
125	18.0	
126		18 @ 1.25
127	0.55	
128	0.7	
129	0.035	
131	1.28	
132		5.4 @ 0.063
133	16.0	
134	0.3	
135	22.0	
136	0.09	

137	2.4	
138	3.0	
139	>25.0	
142	0.5	
143	0.03	
144	0.053	
262	0.07	
263	0.7	
264	0.2	
265	2.0	
266	0.5	
267	0.073	
268	0.029	
269	0.08	
270	0.12	
271	0.07	
272	0.7	
273	1.9	
274	0.18	
275		5.0 @ 0.25
276	0.23	
277	0.04	
278	3.0	
279	0.4	
280	0.18	
281	0.019	
282	0.021	
283	0.35	
284	0.08	
286	19.0	
287	4.0	
288		10.0 @ 6.25
289	0.23	
290	0.054	
291	0.6	
292	0.046	
293	1.9	
294	0.013	
295	1.3	
296	1.6	
1005	0.0004	
1006	0.001	

1007	0.001	
1008	0.001	
1009	0.001	
1010	0.001	
1011	0.001	
1012	0.0015	
1013	0.002	
1014	0.002	
1015	0.002	
1016	0.002	
1017	0.002	
1018	0.002	
1019	0.002	
1020	0.002	
1021	0.002	
1022	0.002	
1023	0.002	
1024	0.002	
1025	0.002	
1026	0.002	
1027	0.002	
1028	0.002	
1029	0.002	
1030	0.002	
1031	0.002	
1032	0.002	
1033	0.002	
1034	0.002	
1035	0.002	
1036	0.002	
1037	0.0022	
1038	0.0025	
1039	0.0026	
1040	0.003	
1041	0.003	
1042	0.003	
1043	0.003	
1044	0.003	
1045	0.003	
1046	0.003	
1047	0.003	
1048	0.003	

1049	0.003	
1050	0.003	
1051	0.003	
1052	0.003	
1053	0.003	
1054	0.003	
1055	0.003	
1056	0.003	
1057	0.003	
1058	0.003	
1059	0.003	
1060	0.0036	
1061	0.004	
1062	0.004	
1063	0.004	
1064	0.004	
1065	0.004	
1066	0.004	
1067	0.004	
1068	0.004	
1069	0.004	
1070	0.004	
1071	0.004	
1072	0.004	
1073	0.004	
1074	0.004	
1075	0.0043	
1076	0.0045	
1077	0.0045	
1078	0.0045	
1079	0.005	
1080	0.005	
1081	0.005	
1082	0.005	
1083	0.005	
1084	0.005	
1085	0.005	
1086	0.005	
1087	0.005	
1088	0.0055	
1089	0.0057	
1090	0.006	

1091	0.006	
1092	0.006	
1093	0.006	
1094	0.006	
1095	0.006	
1096	0.006	
1097	0.006	
1098	0.006	
1099	0.0063	
1100	0.0068	
1101	0.007	
1102	0.007	
1103	0.007	
1104	0.007	
1105	0.007	
1106	0.0073	
1107	0.0075	
1108	0.0075	
1109	0.008	
1110	0.008	
1111	0.008	
1112	0.008	
1113	0.009	
1114	0.009	
1115	0.0098	
1116	0.0093	
1117	0.01	
1118	0.01	
1119	0.01	
1120	0.01	
1121	0.01	
1122	0.011	
1123	0.011	
1124	0.011	
1125	0.012	
1126	0.013	
1127	0.013	
1128	0.017	
1129	0.018	
1130	0.018	
1131	0.02	
1132	0.02	

1133	0.02	
1134	0.02	
1135	0.021	
1136	0.021	
1137	0.021	
1138	0.022	
1139	0.022	
1140	0.023	
1141	0.023	
1142	0.024	
1143	0.027	
1144	0.028	
1145	0.029	
1146	0.029	
1147	0.029	
1148	0.03	
1149	0.03	
1150	0.03	
1151	0.031	
1152	0.036	
1153	0.037	
1154	0.037	
1155	0.039	
1156	0.039	
1157	0.04	
1158	0.06	
1159	0.06	
1160	0.062	
1161	0.063	
1162	0.063	
1163	0.09	
1164	0.093	
1165	0.11	
1166	0.11	
1167	0.12	
1168	0.12	
1169	0.12	
1170	0.13	
1171	0.14	
1172	0.14	
1173	0.15	
1174	0.15	

1175	0.17	
1176	0.18	
1177	0.18	
1178	0.19	
1179	0.19	
1180	0.2	
1181	0.22	
1182	0.25	
1183	0.28	
1184	0.28	
1185	0.28	
1186	0.3	
1187	0.32	
1188	0.35	
1189	0.35	
1190	0.55	
1191	0.65	
1192	1.0	
1193	1.0	
1194	1.6	
1195	1.7	
1196	2.0	
1197	2.2	
1198	2.5	
1199	4.0	
1200	6.1	
1201	8.3	
1202	40.0	
1203		0 @ 0.063
1204	0.05	
1205	0.034	
1206	0.035	
1207	0.068	
1208	0.042	
1209		0 @ 0.063
1210	0.14	
1211	0.28	
1212	0.39	
1213	1.7	
1214	0.75	
1215	0.19	
1216	0.39	

1217	0.32	
1218	0.19	
1219	0.34	
1220	0.2	
1221	0.041	
1222	0.065	
1223	0.28	
1224	0.33	
1225	0.12	
1226	0.046	
1227	0.25	
1228	0.038	
1229	0.049	
1230	0.062	
1231	0.075	
1232	1.2	
1233	0.15	
1234	0.067	
1235	0.045	
1236	0.05	
1237	0.07	
1238	0.8	
1239	0.035	
1240	0.016	
1241	0.047	
1242	0.029	
1243	0.63	
1244	0.062	
1245	0.32	
1246	0.018	
1247	0.017	
1248	0.33	
1249	10.2	
1250	0.013	
1251	0.62	
1252	29.	
1253	0.3	
1254	0.85	
1255	0.69	
1256	0.011	
1257	0.1	
1258	0.12	

1259	16.5	
1260	0.012	
1261	0.019	
1262	0.03	
1263	0.079	
1264	0.21	
1265	0.24	
1266	0.2	
1267	0.29	
1268	0.035	
1269	0.026	
1270	0.026	
1271	0.011	
1272	0.047	
1273	0.029	
1274	0.028	
1275	0.024	
1276	0.029	
1277	0.018	
1278	0.017	
1279	0.028	
1280	0.76	
1281	0.055	
1282	0.17	
1283	0.17	
1284	0.011	
1285	0.027	
1286	0.068	
1287	0.071	
1288	0.013	
1289	0.026	
1290	0.017	
1291	0.013	
1292	0.025	
1293	0.019	
1294	0.011	
1295	0.014	
1296	0.063	
1297	0.029	
1298	0.018	
1299	0.012	
1300	1.0	

1301	0.15	
1302	1.4	
1303	0.26	
1304	0.25	
1305	0.25	
1306	1.2	
1307	3.1	
1308	0.04	
1309	0.24	
1310	1.16	
1311	3.27	
1312	5.0	
1313	6.1	
1314	0.26	
1315	1.67	
1316	3.9	
1317	21.0	
1319		11.0 @ 0.25
1321		11.1 @ 5.0
1322		3.0 @ 0.0063
1323		4.0 @ 0.0063
1324		43.0 @ 0.0008
1325		1.0 @ 0.0063
1326		36.0 @ 0.0008
1327		3.0 @ 0.0063
1328		68.0 @ 0.0063
1329		2.0 @ 0.0063
1330		9.0 @ 0.0063
1331		57.0 @ 0.0008
1332		43.0 @ 0.0008
1333		0 @ 0.0063
1334		50.0 @ 0.0008
1335		38.0 @ 0.0008
1336		45.0 @ 0.0008
1337		0 @ 0.0063
1338		1.0 @ 0.25
1339		0 @ 0.063
1340		9.0 @ 0.063
1341		1.0 @ 0.063
1342		1.0 @ 0.063
1345		13.0 @ 0.25
1347	0.0036	

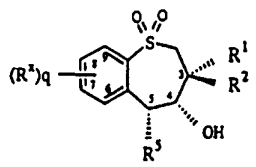
1351	0.44	
1352	0.10	
1353	0.0015	
1354	0.006	
1355	0.0015	
1356	0.22	
1357	0.023	
1358	0.008	
1359	0.014	
1360	0.003	
1361	0.004	
1362	0.019	
1363	0.008	
1364	0.006	
1365	0.008	
1366	0.015	
1367	0.002	
1368	0.005	
1369	0.005	
1370	0.002	
1371	0.004	
1372	0.004	
1373	0.008	
1374	0.007	
1375	0.002	
1449	0.052	
1450	0.039	
1451	0.014	

The examples herein can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Novel compositions of the invention are further illustrated in attached Exhibits A and B.

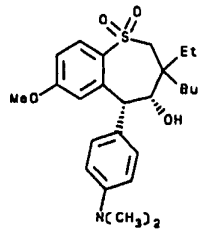
The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

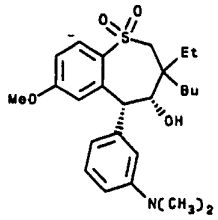
Table C2: Alternative compounds #2 (Families F101-F123)

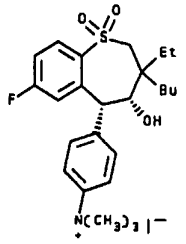


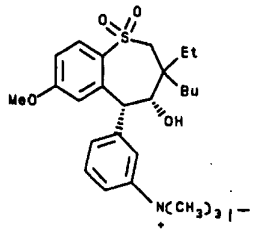
Family	Cpd#	R^1=R^2	R^5	$(R^x)q$
F101	CHOSEN FROM TABLE D *	Ph-	CHOSEN FROM TABLE D
F102	CHOSEN FROM TABLE D	p-F-Ph-	CHOSEN FROM TABLE D
F103	CHOSEN FROM TABLE D	m-F-Ph-	CHOSEN FROM TABLE D
F104	CHOSEN FROM TABLE D	p-CH_3O-Ph-	CHOSEN FROM TABLE D
F105	CHOSEN FROM TABLE D	m-CH_3O-Ph-	CHOSEN FROM TABLE D
F106	CHOSEN FROM TABLE D	p-$(CH_3)_2N$-Ph-	CHOSEN FROM TABLE D
F107	CHOSEN FROM TABLE D	m-$(CH_3)_2N$-Ph	CHOSEN FROM TABLE D
F108	CHOSEN FROM TABLE D	I^-, p-$(CH_3)_3$-N^+-Ph-	CHOSEN FROM TABLE D
F109	CHOSEN FROM TABLE D	I^-, m-$(CH_3)_3$-N^+-Ph-	CHOSEN FROM TABLE D
F110	CHOSEN FROM TABLE D	I^-, p-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE D
F111	CHOSEN FROM TABLE D	I^-, m-$(CH_3)_3$-N^+-CH_2CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE D
F112	CHOSEN FROM TABLE D	I^-, p-(N,N-dimethylpiperazine)-(N')-CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE D
F113	CHOSEN FROM TABLE D	I^-, m-(N,N-dimethylpiperazine)-(N')-CH_2-$(OCH_2CH_2)_2$-O-Ph-	CHOSEN FROM TABLE D
F114	CHOSEN FROM TABLE D	m-F-Ph- p-CH_3O-	CHOSEN FROM TABLE D
F115	CHOSEN FROM TABLE D	3,4,dioxy-methylene-Ph-	CHOSEN FROM TABLE D
F116	CHOSEN FROM TABLE D	m-F-Ph- p-F-Ph-	CHOSEN FROM TABLE D
F117	CHOSEN FROM TABLE D	m-CH_3O- p-F-Ph-	CHOSEN FROM TABLE D
F118	CHOSEN FROM TABLE D	4-pyridine	CHOSEN FROM TABLE D
F119	CHOSEN FROM TABLE D	N-methyl-4-pyridinium	CHOSEN FROM TABLE D
F120	CHOSEN FROM TABLE D	3-pyridine	CHOSEN FROM TABLE D
F121	CHOSEN FROM TABLE D	N-methyl-3-pyridinium	CHOSEN FROM TABLE D
F122	CHOSEN FROM TABLE D	2-pyridine	CHOSEN FROM TABLE D
F123	CHOSEN FROM TABLE D	p-CH_3O_2C-Ph-	CHOSEN FROM TABLE D

Similar families can be generated where $R^1 <> R^2$, such as R^1 = Et and R^2 = n-Bu, but $(R^x)q$ is chosen from table C1.









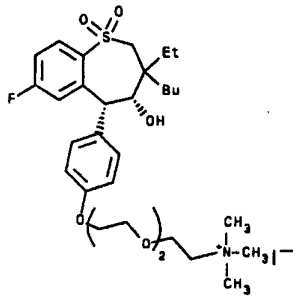
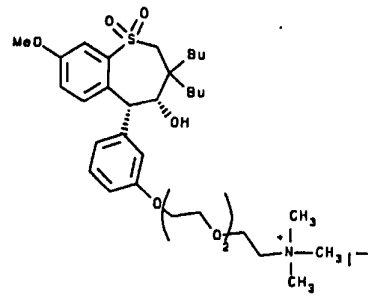
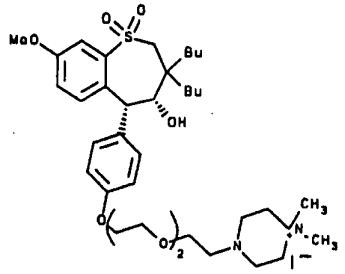
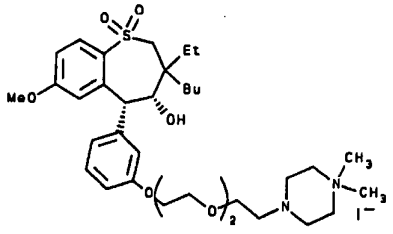
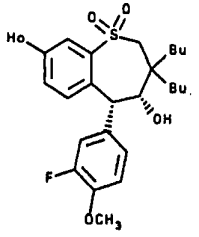


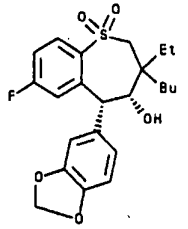
Exhibit B

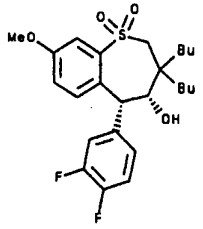


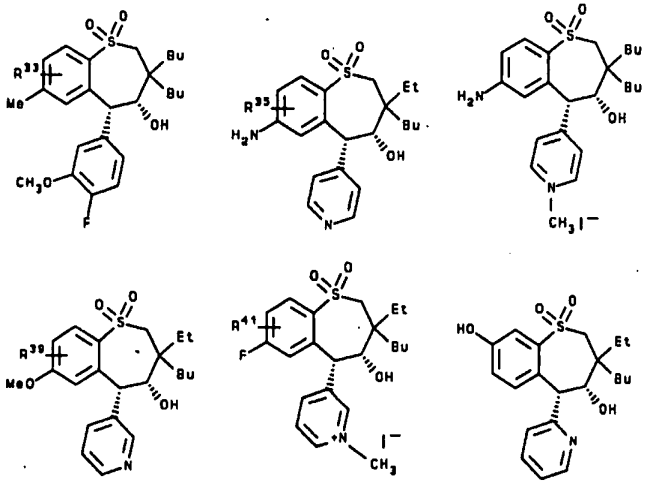






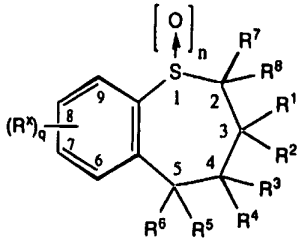






What Is Claimed Is:

1. A compound of formula (I):



(I)

wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^WA^-$, SR^9, $S^+R^9A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13},

$P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR^{11})OR^{14}$, $S^+R^{11}R^{11}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, P(O)R7, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, cycloalkyl, heterocycle, heterocycle, quaternary heterocycle, quaternary heteroaryl, and quaternary heteroarylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR', $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, P(O)R', phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13}, R^{14}, and R^{15} are optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$,

SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR16)OR17$, $P^+R^9R^{10}A^-$, $S^+R^9A^-$, and C(O)OM,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring;

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heterocycle, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13}, $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, NR"C(O)R", $C(O)NR^{13}R^{14}$, NR14C(O)R13, C(O)OM, COR^{13}, OR^{18}, $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR")OR"$, $P^+R^9R^{11}R^{12}A^-$, $S^+R"R"A^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituent selected from the group

consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, P(O)R13, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or P(O)R';

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR")OR"$, $S^+R"R"A^-$, and $N^+R^9R^{11}R^{12}A^-$,

provided that both R^5 and R^6 cannot be hydrogen, OH, or SH and when R^5 is OH, R^1, R^2, R^3, R^4, R^7 and R^8 cannot be all hydrogen;

provided that when R' or R' is phenyl, only one of R' or R' is H;

provided that when q = 1 and R' is styryl, anilido, or anilinocarbonyl, only one of R' or R' is alkyl.

2. A compound of claim 1, wherein R^5 and R^6 are independently selected from the group consisting of H,

aryl, heterocycle, quaternary heterocycle, and quaternary heteroaryl,

wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, P(O)R7, $P^+R^7R^8A^-$, or phenylene,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR')OR'$.

3. A compound of claim 2, wherein R' or R' has the formula

$$-Ar-(R^y)_t$$

wherein:

t is an integer from 0 to 5;

Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; and

one or more R^y are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

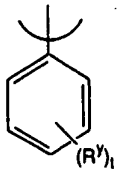
wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S^+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR')OR'$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O,

NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, P(O)R', $P^+R^7R^8A^-$, or phenylene.

4. A compound of claim 3, wherein R^5 or R^6 has the formula (II)



(II)

5. A compound of claim 4, wherein n is 1 or 2.

6. A compound of claim 5, wherein one of R^7 or R^8 is H and the other of R' or R' is alkyl.

7. A compound of claim 5, wherein both R^7 and R^8 are H.

8. A compound of claim 7, wherein R^1 and R^2 are independently selected from the group consisting of H and alkyl.

9. A compound of claim 8, wherein said alkyl is a C_1-C_{10} alkyl.

10. A compound of claim 8, wherein R^1 and R^2 are both alkyl.

11. A compound of claim 10, wherein said alkyl is a C_1-C_{10} alkyl.

12. A compound of claim 11, wherein said alkyl is a C_2-C_6 alkyl.

13. A compound of claim 12, wherein said alkyl is a C_2-C_4 alkyl.

14. A compound of claim 13, wherein said alkyl is independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

15. A compound of claim 8, wherein R^1 and R^2 are each n-butyl.

16. A compound of claim 8, wherein one of R1 and R2 is ethyl and the other of R^1 and R^2 is n-butyl.

17. A compound of claim 15, wherein q is 1, 2, or 3.

18. A compound of claim 16, wherein q is 1, 2, or 3.

19. A compound of claim 17, wherein q is 1 or 2.

20. A compound of claim 19, wherein q is 1.

21. A compound of claim 18, wherein q is 1 or 2.

22. A compound of claim 21, wherein q is 1.

23. A compound of claim 19, wherein R^3 and R^4 are independently selected from the group consisting of H and OR'.

24. A compound of claim 21, wherein R^3 and R^4 are independently selected from the group consisting of H and OR'.

25. A compound of claim 23, wherein R' is H.

26. A compound of claim 24, wherein R' is H.

27. A compound of claim 25, wherein one or more R^X are in the 7-, 8-, or 9-position of the benzo ring of formula (I).

28. A compound of claim 26, wherein said R^X is in the 7-, 8-, or 9- position of the benzo ring of formula (I).

29. A compound of claim 27, wherein said R^X are in the 7- and 9- positions of the benzo ring of formula (I).

30. A compound of claim 28, wherein said R^X is in the 7-position of the benzo ring of formula (I).

31. A compound of claim 29, wherein said one or more R^X are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{14}C(O)R^{13}$, and $NR^{14}C(O)R^{13}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR'R^{10}$, $PO(OR^{14})OR^{13}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R'R^{10}A^-$, or C(O)OM, and

wherein in R^X, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid,

peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R'$.

32. A compound of claim 30, wherein said R^X is selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{14}C(O)R^{13}$, and $NR^{14}C(O)R^{13}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR'R^{10}$, $PO(OR^{14})OR^{13}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R'R^{10}A^-$, or C(O)OM, and

wherein in R^X, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R'$.

33. A compound of claim 31, wherein said one or more Rx are independently selected from the group consisting of polyether, OR^{13}, $NR^{13}R^{14}$, and $N^+R^9R^{11}R^{12}A^-$.

34. A compound of the claim 32, wherein said Rx is selected from the group consisting of polyether, OR^{13}, $NR^{13}R^{14}$, and $N^+R^9R^{11}R^{12}A^-$.

35. A compound of claim 33, wherein said one or more Rx are independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$.

36. A compound of claim 34, wherein said R^x is independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$.

37. A compound of claim 35, wherein R^{13} and R^{14} each methyl.

38. A compound of the claim 36, wherein R^{13} and R^{14} each methyl.

39. A compound of claim 31, wherein one or more R^y are independently in the 3- or the 4-position of the phenyl ring of formula (II).

40. A compound of claim 32, wherein one or more Ry are independently in the 3- or the 4- position of the phenyl ring of formula (II).

41. A compound of claim 39, wherein t is 1 or 2.

42. A compound of claim 40, wherein t is 1 or 2.

43. A compound of claim 41, wherein said one or more R^y are independently selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

44. A compound of claim 42, wherein said R^y is independently selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

45. A compound of claim 43, wherein said one or more R^y are independently selected from the group consisting of alkyl, polyether, fluoride, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

46. A compound of claim 44 wherein said R^y is independently selected from the group consisting of alkyl, polyether, fluoride, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

47. A compound of claim 45, wherein said R^{13} and R^{14} are alkyl,

wherein alkyl can be further substituted with $SO'R'$, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

48. A compound of claim 46, wherein said R' and R^{10} are alkyl,

wherein alkyl can be further substituted with $SO'R'$, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

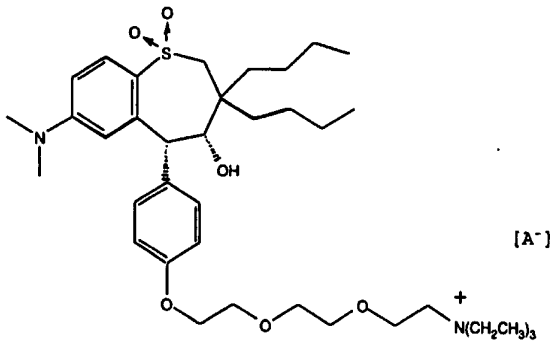
49. A compound of claim 47, wherein n is 2.

50. A compound of claim 48, wherein n is 2.

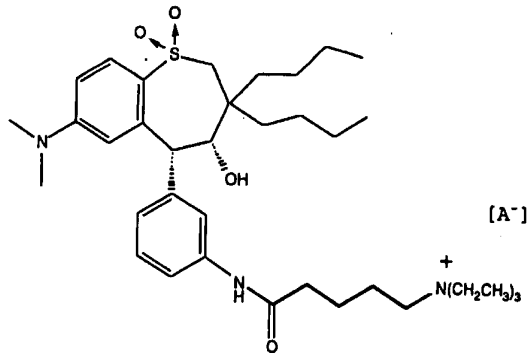
51. A compound of claim 49, wherein said OH group is in a *syn* relationship to said structure of formula (II).

52. A compound of claim 50, wherein said OH group is in a *syn* relationship to said structure of formula (II).

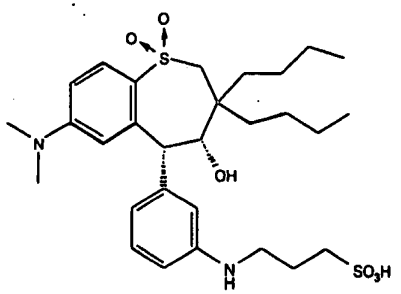
53. A compound of claim 51, having the formula:



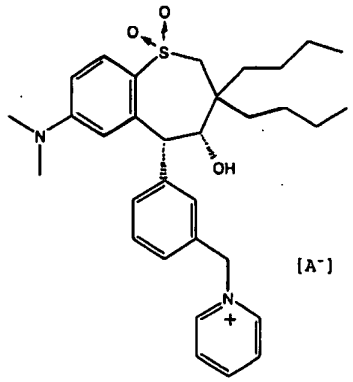
54. A compound of claim 51, having the formula:



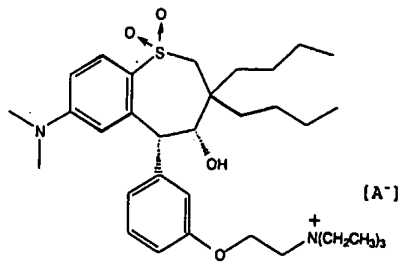
55. A compound of claim 51, having the formula:



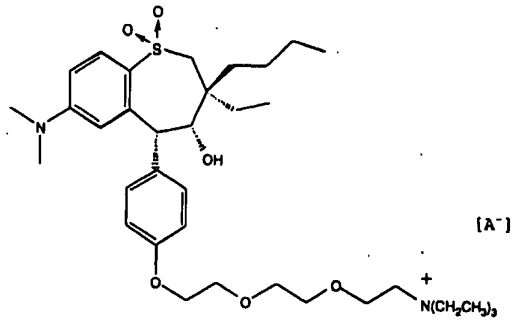
56. A compound of claim 51, having the formula:



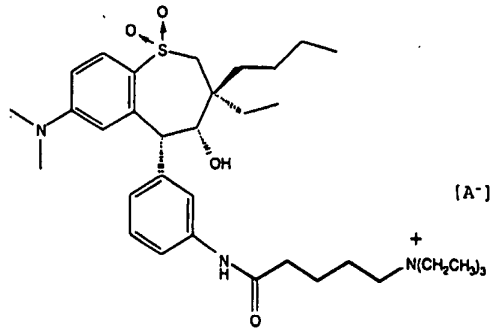
57. A compound of claim 51, having the formula:



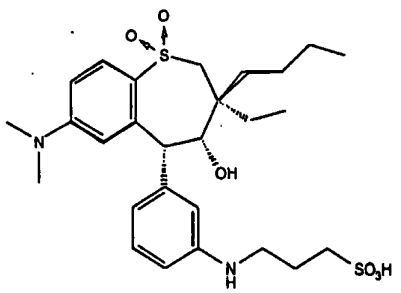
58. A compound of claim 52, having the formula:



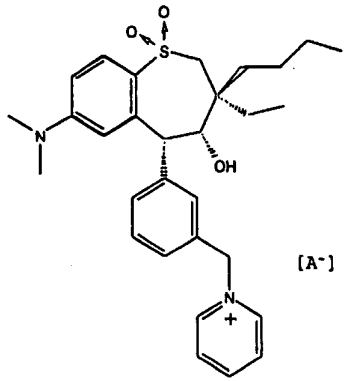
59. A compound of claim 52, having the formula:



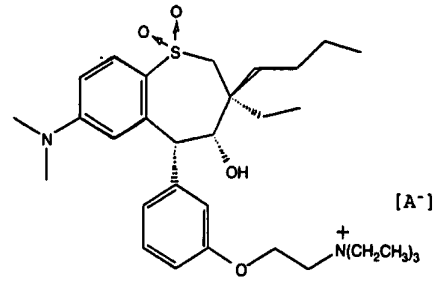
60. A compound of claim 52, having the formula:



61. A compound of claim 52, having the formula:



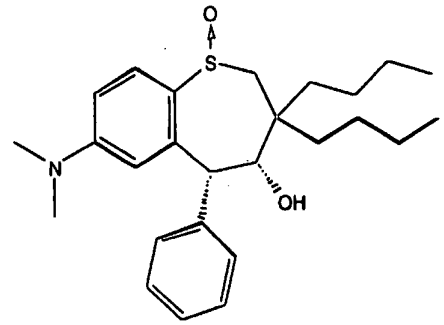
62. A compound of claim 52, having the formula:



63. A compound of claim 31, wherein n is 1.

64. A compound of claim 63, wherein R^7 is H.

65. A compound of claim 64, having the formula



66. A compound of claim 4, wherein R^1 and R^2 are independently selected from the group consisting of H and alkyl.

67. A compound of claim 66, wherein said alkyl is C_1-C_{10} alkyl.

68. A compound of claim 67, wherein said alkyl is C_2-C_7 alkyl.

69. A compound of claim 68, wherein said alkyl is C_1-C_4 alkyl.

70. A compound of claim 69, wherein R^1 and R^2 are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

71. A compound of claim 4, wherein R^2 and R^4 are independently selected from the group consisting of H and OR^9.

72. A compound of claim 71, wherein R^9 is H.

73. A compound of claim 4, wherein n is 2.

74. A compound of claim 3, wherein R^2 and R^4 are independently selected from the group consisting of H and OR^9.

75. A compound of claim 74, wherein R^9 is H.

76. A compound of claim 3, wherein one of R^7 or R^8 is H.

77. A compound of claim 76, wherein both R^7 and R^8 are H.

78. A compound of claim 3, wherein said one or more R^x are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR''C(O)R''$, and $NR''C(O)R''$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9,

$S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR'R''$, $PO(OR'')OR''$, $P^+R^9R^{11}R^{12}A^-$, $S^+R'R''A^-$, or $C(O)OM$, and

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R''$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$.

79. A compound of claim 78, wherein said one or more R^x are independently selected from the group consisting of polyether, OR'', $NR''R''$, and $N^+R^9R^{11}R^{12}A^-$.

80. A compound of claim 79, wherein said one or more R^x are independently selected from the group consisting of OR'' and $NR''R''$.

81. A compound of claim 80, wherein R'' and R'' are each methyl.

82. A compound of claim 3, wherein one or more R^y are independently in the 3- or the 4-position of the phenyl ring of formula (II).

83. A compound of claim 82, wherein one or more R^y is selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, NR^9R^{10}, and $NC(O)R^9$,

wherein alkyl and polyether can be substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

84. A compound of claim 83, wherein R^9 and R^{10} are alkyl.

85. A compound of claim 84, wherein one or more R^y is selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, NR^9R^{10}, and $NC(O)R^9$.

86. A compound of claim 1, wherein said one or more R^x are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{14}C(O)R^{13}$, and $NR^{14}C(O)R^{13}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{14})OR^{13}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$.

87. A compound of claim 1, wherein n is 1 or 2.

88. A compound of claim 87, wherein n is 2.

89. A compound of claim 1, wherein R^1 and R^2 are independently selected from the group consisting of H and alkyl.

90. A compound of claim 89, wherein said alkyl is C_1-C_{10} alkyl.

91. A compound of claim 90, wherein said alkyl is C_2-C_7 alkyl.

92. A compound of claim 91, wherein said alkyl is C_2-C_4 alkyl.

93. A compound of claim 92, wherein R^1 and R^2 are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

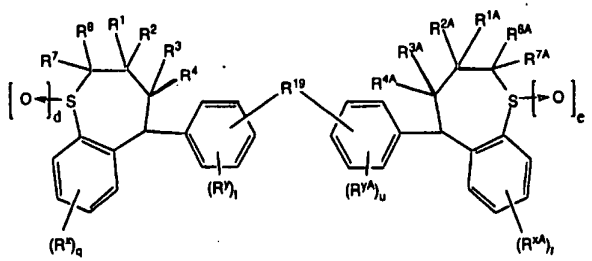
94. A compound of claim 1, wherein R^3 and R^4 are independently selected from the group consisting of H and OR^9.

95. A compound of claim 94, wherein R^9 is H.

96. A compound of claim 1, wherein one of R^7 or R^8 is H.

97. A compound of claim 96, wherein both R^7 and R^8 are H.

98. A compound of the formula (III)



(III)

wherein :

q and r are independently integers from 0 to 4;

d and e are independently integers from 0 to 2;

t and u are independently integers from 0 to 4;

R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^WA^-$, SR^9, $S^+R^9A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene, or

R^{1A} and R^{2A} taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene;

R^3, R^{3A}, R^4, and R^{4A} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$, or

R^{3A} and R^{4A} together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation;

R^7, R^{7A}, R^8, and R^{8A} are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X and R^{XA} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heterocycle, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13}, $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $NR^{11}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, NR14C(O)R13, C(O)OM, COR^{13}, OR^{18}, $S(O)_nNR^{18}$, $NR^{13}R^{18}$,

$NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR'')OR''$, $P^+R^9R^{11}R^{12}A^-$, $S^+R'R''A^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^x and R^{xx}, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, P(O)R13, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or P(O)R';

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen,

oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S^+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

R'' is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, quatarnary heterocycle, quaternary heteroaryl, or aryl,

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S^+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$;

wherein one or more R^y and R^{yy} are independently selected from from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the

group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR^{13})OR^{14}$, $S^-R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR')OR'$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene.

99. A compound of claim 98, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and alkyl.

100. A compound of claim 99, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and C_1-C_{10} alkyl.

101. A compound of claim 100, wherein said alkyl is a C_1-C_4 alkyl.

102. A compound of claim 101, wherein R^1, R^{1A}, R^2, and R^{2A} are independently C_1-C_4 alkyl.

103. A compound of claim 102, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

104. A compound of claim 98, wherein R^3, R^{3A}, R^4, and R^{4A} are independently selected from the group consisting of H and OR^7.

105. A compound of claim 104, wherein R^7 is H.

106. A compound of claim 98, wherein R^3, R^{3A}, R^4, and R^{4A} are H.

107. A compound of claim 98, wherein d and e are independently 1 or 2.

108. A compound of claim 107, wherein d and e are both 2.

109. A compound of claim 98, wherein one or more R^X and one or more R^{xA} are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{11}C(O)R^{11}$, and $NR^{11}C(O)R^{11}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{11})OR^{11}$, $P^+R^9R^{11}R^{12}A^-$, $S^-R^9R^{10}A^-$, or C(O)OM, and

wherein in R^X, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid,

peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$.

110. A compound of claim 98, wherein one or more R^y and one or more R^{ya} are independently selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

111. A compound of claim 98, wherein R^{13} is selected from the group consisting of alkane diyl, polyalkane diyl, alkoxy diyl, and polyalkoxy diyl, wherein alkane diyl and polyalkane diyl can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, or phenylene.

112. A compound of claim 111, wherein R^{13} is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}$, S, SO, SO_2, $S^+R^9R^{10}$, PR^9, $P^+R^9R^{10}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, or polyalkyl.

113. A compound of claim 112, wherein R^1, R^{1a}, R^2, and R^{2a} are independently selected from the group consisting of H and alkyl.

114. A compound of claim 113, wherein R^3, R^{3a}, R^4, and R^{4a} are independently selected from the group consisting of H and OR^9.

115. A compound of claim 114, wherein R^9 is H.

116. A compound of claim 115, wherein R^1, R^{1a}, R^2, and R^{2a} are each H.

117. A compound of claim 116, wherein d and e are independently 1 or 2.

118. A compound of claim 117, wherein one or more R^x and one or more R^{xa} are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{14}C(O)R^{13}$, and $NR^{14}C(O)R^{13}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

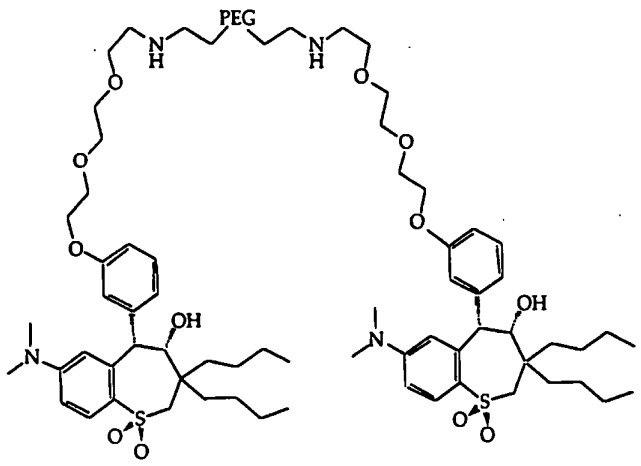
wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$.

119. A compound of claim 118, wherein one or more R^y and one or more R^{ya} are independently selected from

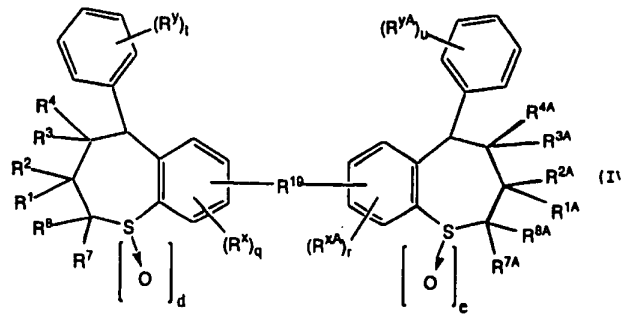
the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13}, wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

120. A compound of claim 119, having the formula:



PEG = 3400 molecular weight polyethylene glycol polymer chain

121. A compound of the formula (IV)



wherein :

q and r are independently integers from 0 to 3;

d and e are independently integers from 0 to 2;

t and u are independently integers from 0 to 5;

R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^WA^-$, SR^9, $S^+R^9A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene, or

R^{1A} and R^{2A} taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene;

R^1, R^{1A}, R^4, and R^{4A} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$, or

R^{3A} and R^{4A} together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation;

R^7, R^{7A}, R^8, and R^{8A} are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X and R^{XA} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heterocycle, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$,

SO_3R^{13}, $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, NR14C(O)R13, C(O)OM, COR^{13}, OR^{18}, $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{14})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^X and R^{XA}, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, P(O)R13, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more

groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR^{11})OR^{14}$, $S^-R^{11}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

R^{11} is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, quatarnary heterocycle, quaternary heteroaryl, or aryl,

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR^{11})OR^{14}$, $S^-R^{11}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$;

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo,

$CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR')OR'$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R'$, $P^+R^7R^8A^-$, or phenylene.

122. A compound of claim 121, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and alkyl.

123. A compound of claim 122, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and C_1-C_{10} alkyl.

124. A compound of claim 123, wherein said alkyl is a C_1-C_4 alkyl.

125. A compound of claim 124, wherein R^1, R^{1A}, R^2, and R^{2A} are independently C_1-C_4 alkyl.

126. A compound of claim 125, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

127. A compound of claim 125, wherein R^2, R^{2A}, R^4, and R^{4A} are independently selected from the group consisting of H and OR'.

128. A compound of claim 127, wherein R' is H.

129. A compound of claim 121, wherein R^2, R^{2A}, R^4, and R^{4A} are H.

130. A compound of claim 121, wherein d and e are independently 1 or 2.

131. A compound of claim 130, wherein d and e are both 2.

132. A compound of claim 121, wherein one or more R^x and one or more R^{xx} are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{14}C(O)R^{13}$, and $NR^{14}C(O)R^{13}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{14})OR^{13}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$.

133. A compound of claim 121, wherein one or more R^y and one or more R^{yy} are independently selected from the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

134. A compound of claim 121, wherein R^{13} is selected from the group consisting of alkane diyl, polyalkane diyl, alkoxy diyl, and polyalkoxy diyl, wherein alkane diyl and polyalkane diyl can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, or phenylene.

135. A compound of claim 134, wherein R^{13} is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}$, S, SO, SO_2, $S^+R^9R^{10}$, PR^9, $P^+R^9R^{10}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, or polyalkyl.

136. A compound of claim 135, wherein R^1, R^{1a}, R^2, and R^{2a} are independently selected from the group consisting of H and alkyl.

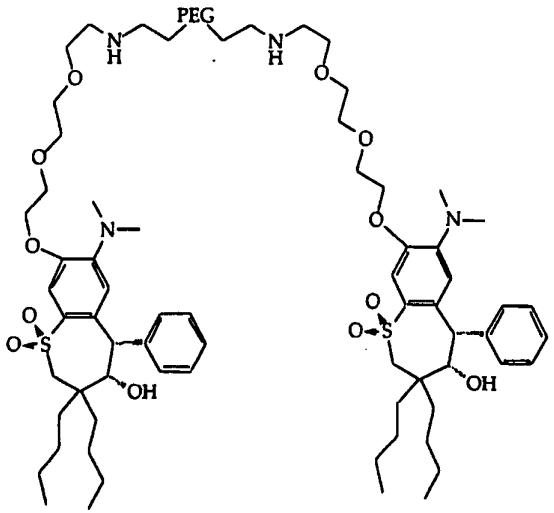
137. A compound of claim 136, wherein R^3, R^{3a}, R^4, and R^{4a} are independently selected from the group consisting of H and OR^9.

138. A compound of claim 137, wherein R^9 is H.

139. A compound of claim 138, wherein R^3, R^{3a}, R^4, and R^{4a} are each H.

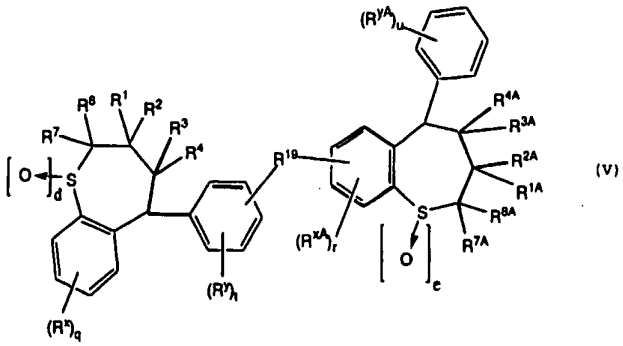
140. A compound of claim 139, wherein d and e are independently 1 or 2.

141. A compound of claim 140, having the formula:



PEG = 3400 molecular weight polyethylene glycol polymer chain

142. A compound of formula (V)



(V)

wherein :

q is an integer from 0 to 4;

r is an integer from 0 to 3;

d and e are independently integers from 0 to 2;

t is an integer from 0 to 4;

u is an integer from 0 to 5;

R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituent selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^WA^-$, SR^9, $S^+R^9A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, polyalkyl, aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene, or

R^{1A} and R^{2A} taken together with the carbon to which they are attached form C_3-C_{10} cycloalkylidene;

R^3, R^{3A}, R^4, and R^{4A} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$, or

R^{3A} and R^{4A} together form =O, =NOR^{11}, =S, =NNR^{11}R^{12}, =NR^{9}, or =CR^{11}R^{12},

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^{9}, NR^{9}R^{10}, SR^{9}, S(O)R^{9}, SO$_2$R^{9}, SO$_3$R^{9}, CO$_2$R^{9}, CN, halogen, oxo, and CONR^{9}R^{10}, wherein R^{9} and R^{10} are as defined above, provided that both R^{3} and R^{4} cannot be OH, NH2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

wherein A$^-$ is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation;

R^{7}, R^{7A}, R^{8}, and R^{8A} are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^{X} and R^{XA} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heterocycle, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, NR^{13}R^{14}, SR^{13}, S(O)R^{13}, S(O)$_2$R^{13}, SO$_3$R^{13}, S$^+$R^{13}R^{14}A-, NR^{13}OR^{14}, NR^{13}NR^{14}R^{15}, NO$_2$, CO$_2$R^{13}, CN, OM, SO$_2$OM, SO$_2$NR^{13}R^{14}, NR^{14}C(O)R^{13}, C(O)NR^{13}R^{14}, NR14C(O)R13, C(O)OM, COR^{13}, OR^{18}, S(O)$_n$NR^{18}, NR^{13}R^{18}, NR^{18}OR^{14}, N$^+$R^{9}R^{11}R^{12}A$^-$, P$^+$R^{9}R^{11}R^{12}A$^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^{9}, NR^{9}R^{10}, N$^+$R^{9}R^{11}R^{12}A$^-$, SR^{9}, S(O)R^{9}, SO$_2$R^{9}, SO$_3$R^{9}, oxo, CO$_2$R^{9},

CN, halogen, CONR^{9}R^{10}, SO$_2$OM, SO$_2$NR^{9}R^{10}, PO(OR^{16})OR^{17}, P$^+$R^{9}R^{11}R^{12}A$^-$, S$^+$R^{9}R^{10}A$^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heterocycle, alkyl quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituent selected from the group consisting of OR^{9}, NR^{9}R^{10}, N$^+$R^{9}R^{11}R^{12}A$^-$, SR^{9}, S(O)R^{9}, SO$_2$R^{9}, SO$_3$R^{9}, oxo, CO$_2$R^{9}, CN, halogen, CONR^{9}R^{10}, SO$_3$R^{9}, SO$_2$OM, SO$_2$NR^{9}R^{10}, PO(OR^{16})OR^{17}, and C(O)OM,

wherein in R^{X} and R^{XA}, one or more carbons are optionally replaced by O, NR^{13}, N$^+$R^{13}R^{14}A-, S, SO, SO$_2$, S$^+$R^{13}A-, PR^{13}, P(O)R13, P$^+$R^{13}R^{14}A-, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^{9}, N$^+$R^{9}R^{10}A-, S, SO, SO$_2$, S$^+$R^{9}A-, PR^{9}, P$^+$R^{9}R^{10}A-, or P(O)R^{9};

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, NR^{13}R^{14}, SR^{13}, S(O)R^{13}, SO$_2$R^{13}, SO$_3$R^{13}, NR^{13}OR^{14}, NR^{13}NR^{14}R^{15}, NO$_2$, CO$_2$R^{13}, CN, OM, SO$_2$OM, SO$_2$NR^{13}R^{14}, C(O)NR^{13}R^{14}, C(O)OM, COR^{13}, P(O)R^{13}R^{14}, P$^+$R^{13}R^{14}R15A-, P(OR^{11})OR^{14}, S$^+$R^{11}R^{14}A$^-$, and N$^+$R^{9}R^{11}R^{12}A$^-$,

R^{15} is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate,

amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, phenylene, heterocycle, quaternary heterocycle, quaternary heteroaryl, or aryl,

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S^+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$;

wherein one or more R^{9} and R^{9A} are independently selected from from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocycle can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A^-$, $P(OR'')OR''$, $S^+R''R''A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR')OR''$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R'$, $P^+R^7R^8A^-$, or phenylene.

143. A compound of claim 142, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and alkyl.

144. A compound of claim 143, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and C_1-C_{10} alkyl.

145. A compound of claim 144, wherein said alkyl is a C_2-C, alkyl.

146. A compound of claim 145, wherein R^1, R^{1A}, R^2, and R^{2A} are independently C_2-C_4 alkyl.

147. A compound of claim 146, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of ethyl, n-propyl, n-butyl, and isobutyl.

148. A compound of claim 142, wherein R^1, R^{1A}, R^4, and R^{4A} are independently selected from the group consisting of H and OR'.

149. A compound of claim 148, wherein R' is H.

150. A compound of claim 142, wherein R', R'A, R', and R'A are H.

151. A compound of claim 142, wherein d and e are independently 1 or 2.

152. A compound of claim 151, wherein d and e are both 2.

153. A compound of claim 142, wherein one or more R^X and one or more R^{XA} are independently selected from the group consisting of alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR^{13}, $NR^{13}R^{14}$, $NR^{13}NR^{14}R^{15}$, $N^+R^9R^{11}R^{12}A^-$, SR^{13}, $S^+R^{13}R^{14}$, CO_2R^{13}, $NR^{14}C(O)R^{13}$, and $NR^{14}C(O)R^{13}$,

wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$ SO_3OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or C(O)OM, and

wherein in R^X, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A^-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, or $P(O)R^9$.

154. A compound of claim 142, wherein one or more R^Y and one or more R^{YA} are independently selected from

the group consisting of alkyl, polyether, fluoride, chloride, bromide, iodide, $NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, and OR^{13},

wherein alkyl and polyether can be further substituted with SO_3R^9, $N^+R^9R^{11}R^{12}A^-$, and quaternary heteroaryl.

155. A compound of claim 142, wherein R^{19} is selected from the group consisting of alkane diyl, polyalkane diyl, alkoxy diyl, and polyalkoxy diyl, wherein alkane diyl and polyalkane diyl can optionally have one or more carbon replaced by O, NR7, N+R7R8, S, SO, SO2, S+R7R8, PR7, P+R7R8, or phenylene.

156. A compound of claim 155, wherein R^{19} is selected from the group consisting of alkoxy diyl and polyalkoxydiyl wherein one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}$, S, SO, SO_2, $S^+R^9R^{10}$, PR^9, $P^+R^9R^{10}$, phenylene, amino acid, peptide, polypeptide, carbohydrate, or polyalkyl.

157. A compound of claim 156, wherein R^1, R^{1A}, R^2, and R^{2A} are independently selected from the group consisting of H and alkyl.

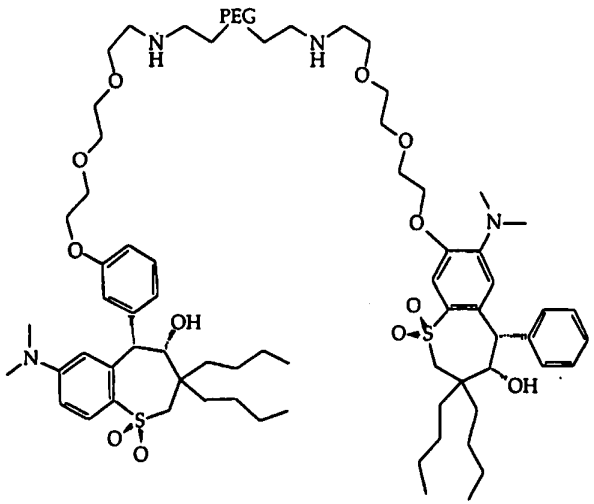
158. A compound of claim 157, wherein R^3, R^{3A}, R^4, and R^{4A} are independently selected from the group consisting of H and OR^9.

159. A compound of claim 158, wherein R^9 is H.

160. A compound of claim 159, wherein R^3, R^{3A}, R^4, and R^{4A} are each H.

161. A compound of claim 160, wherein d and e are independently 1 or 2.

162. A compound of claim 161, having the formula:



PEG = 3400 molecular weight polyethylene glycol polymer chain

163. A pharmaceutical composition comprising an anti-hyperlipidemic condition effective amount of a compound of formula (I) of claim 1, and a pharmaceutically acceptable carrier.

164. A pharmaceutical composition comprising an anti-atherosclerotic effective amount of a compound of formula (I) of claim 1, and a pharmaceutically acceptable carrier.

165. A pharmaceutical composition comprising an anti-hypercholerterolemia effective amount of a compound of formula (I) of claim 1, and a pharmaceutically acceptable carrier.

166. A method for the prophylaxis or treatment of a hyperlipidemic condition comprising administering to

a patient in need thereof a composition of claim 164 in unit dosage form.

167. A method for the prophylaxis or treatment of an atherosclerotic condition comprising administering to a patient in need thereof a composition of claim 165 in unit dosage form.

168. A method for the prophylaxis or treatment of hypercholerterolemia comprising administering to a patient in need thereof a composition of claim 166 in unit dosage form.

INTERNATIONAL SEARCH REPORT

Interm. .al Application No
PCT/US 97/04076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D337/08 C07D409/10 · C08G65/329 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 211 258 A (BOEHRINGER) 4 November 1970 see page 1; claims; example 5 ---	1, 163-165
P,X	WO 96 08484 A (MONSANTO) 21 March 1996 see the whole document -----	1-30, 163-165

☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"B" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 1997	04. 08. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Authorized officer Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In' ational application No.
PCT/US 97/04076

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 166-168
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ..al Application No
PCT/US 97/04076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1211258 A	04-11-70	CH 512429 A	15-09-71
		CH 512502 A	15-09-71
		CH 513111 A	30-09-71
		DE 1593760 A	08-06-72
		FR 8052 M	29-06-70
		FR 1603343 A	05-04-71
WO 9608484 A	21-03-96	AU 3373695 A	29-03-96
		EP 0781278 A	02-07-97